CLINICAL STUDY REPORT

A Phase II, Open-Label, Randomized Study of Immunoconjugate L-DOS47 in Combination with Vinorelbine/Cisplatin Versus Vinorelbine/Cisplatin Alone in Patients with Lung Adenocarcinoma

Sponsor Protocol No.:	LDOS003
Sponsor:	Helix BioPharma Corp.
Coordinating Investigator:	Cezary Szczylik, MD, PhD Europejskie Centrum Zdrowia Otwock 14/18 Borowa Street 05-400 Otwock Poland
Study Drug Name:	L-DOS47
Development Phase:	II
Study Initiation Date:	19 February 2019
Study Early Termination Date:	28 April 2020
Report Date:	28 September 2023
Sponsor Signatory:	Brenda Lee +1 (416) 809-2101 blee@helixbiopharma.com

The study was conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki, and with other applicable regulatory requirements.

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Brenda Lee, M.Sc.
Director, Clinical Operations

Date

DocuSigned by Gary Renshaw
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Frank Gary Renshaw, D.O.
Chief Medical Officer

Date

DocuSigned by Kim Gaspar
I approve this document
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Kim Gaspar, PhD
Director, Quality Assurance

Date

2. SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
Helix BioPharma Corp.</td><td rowspan="3">Individual Study Table Referring to Part of the Document
Volume:
Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
L-DOS47</td></tr>
<tr><td>Name of Active Ingredient:
L-DOS47, an immunoconjugate targeting the enzyme jack bean urease to the tumour antigen CEACAM6.</td></tr>
<tr><td colspan="3">Title of study: A Phase II, Open-Label, Randomized Study of Immunoconjugate L-DOS47 in Combination with Vinorelbine/Cisplatin Versus Vinorelbine/Cisplatin Alone in Patients with Lung Adenocarcinoma</td></tr>
<tr><td colspan="3">Investigators:
Cezary Szczylik, MD, PhD
Dominika Paradowska, MD
Igor Bondarenko, MD
Andrii Kurochkin, MD
Serhii Shevnia, MD</td></tr>
<tr><td colspan="3">Study centres:
Europejskie Centrum Zdrowia Otwock – Otwock, Poland
Jagiellońskie Centrum Innowacji – Kraków, Poland
Dnipropetrovsk City Multi-Field Clinical Hospital #4 – Dnipro, Ukraine
Sumy Regional Clinical Oncological Centre – Sumy, Ukraine
Vinnytsya Regional Clinical Oncological Centre – Vinnytsia, Ukraine</td></tr>
<tr><td colspan="3">Publication: None</td></tr>
<tr><td colspan="3">Studied period (years):
Date of first enrolment: 19 February 2019
Date of last patient visit: 06 May 2020</td></tr>
<tr><td colspan="3">Phase of development: II</td></tr>
<tr><td colspan="3">Objectives:
<u>Primary objectives</u>
The primary objectives of this study were to determine the:
• Safety and tolerability of L-DOS47 in combination treatment with vinorelbine/cisplatin.
• Dose limiting toxicities (DLTs) of L-DOS47 in combination treatment with vinorelbine/cisplatin.</td></tr>
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- Maximum tolerated dose (MTD) and recommended Part 2 dose of L-DOS47 in combination treatment with vinorelbine/cisplatin.
- Preliminary efficacy of L-DOS47 by comparing the time to disease progression (TTP) of L-DOS47 in combination with vinorelbine/cisplatin to vinorelbine/cisplatin alone in patients with lung adenocarcinoma.

Secondary objectives

Secondary objectives were to:

- Determine the preliminary efficacy of L-DOS47 by comparing the objective response rate of L-DOS47 in combination with vinorelbine/cisplatin to vinorelbine/cisplatin alone in patients with lung adenocarcinoma. Response Evaluation Criteria in Solid Tumours [RECIST] version 1.1 criteria will be used to determine the objective response rate [1].
- Compare the safety and tolerability of L-DOS47 in combination with vinorelbine/cisplatin to vinorelbine/cisplatin alone in patients with lung adenocarcinoma.
- Compare the overall survival (OS) of patients administered L-DOS47 in combination with vinorelbine/cisplatin to patients administered vinorelbine/cisplatin alone.

Methodology:

This was a Phase II, open-label, randomised study in male and female patients aged ≥ 18 years old with metastatic lung adenocarcinoma. The staging was to have been conducted according to Tumour Node Metastases (TNM), 8th Edition [2].

In Part 1 of the study (Dose Escalation), patients received 8 doses of L-DOS47 over 4 cycles. On Day 1 and Day 8 of each cycle, L-DOS47 (administered as an intravenous [IV] infusion) was administered 24 hours before chemotherapy. In Part 2 of the study (Randomised Treatment), patients were to have been randomly assigned to receive L-DOS47 in combination with vinorelbine/cisplatin or vinorelbine/cisplatin alone.

Screening took place within 21 days of the first treatment visit. Treatment visits occurred over 4 cycles and an End-of-Treatment Visit after completion of the last 21-day cycle of study treatment.

Follow-up Visits for disease progression were conducted by radiologic assessments every 6 weeks (± 7 days) until one of the following occurred: disease progression, patient initiates non-study cancer treatment, patient withdraws consent, or becomes lost-to-follow-up.

Survival data was captured by telephone call every 30 days (± 7 days) and patients were followed until death, or until the study is terminated.

Part 1 - Dose Escalation:

The Continual Reassessment Method was used to find the maximum tolerated dose (MTD) and the 3+3 algorithm was used for dose escalation. Up to **18** patients were to have been enrolled to receive L-DOS47 in combination with vinorelbine/cisplatin. Patients were recruited into 3 cohorts. An initial cohort of 3 patients was enrolled at a starting dose of **6** μg/kg; a second cohort of 3 patients was enrolled at a dose **9** μg/kg and a third cohort of 3 patients was enrolled

at a dose of **12** μg/kg. If a patient in any cohort experiences a DLT, then an additional 3 patients would have been enrolled into the cohort.

If a patient had a DLT at the starting dose of **6** μg/kg, 3 additional patients would have been enrolled at a dose of **3** μg/kg.

If two DLTs occur at any dose level, that dose was to be defined as not tolerated and the MTD would be defined as the preceding dose.

A DLT was defined as any NCI (National Cancer Institute) Common Terminology Criteria for Adverse Events (CTCAE; v 4.03) ≥ Grade 3 non-haematologic and any ≥ Grade 4 haematologic adverse event (AE) that was at least possibly related to L-DOS47 (possibly, probably, or definitely related) occurring ≤ 3 weeks after commencing L-DOS47 treatment in the opinion of the Investigator.

The decision for dose escalation to the next dose level was to be made after all patients in the cohort had 3 weeks of treatment and safety data was reviewed by the Trial Steering Committee (TSC).

If MTD was not reached, the TSC would have considered the **12** μg/kg as the dose used in the second part of the study.

Part 2 – Randomised Treatment:
After the MTD of L-DOS47 in combination with vinorelbine/cisplatin was determined, **118** patients were to have been randomised (1:1 randomisation) to receive L-DOS47 in combination with vinorelbine/cisplatin or vinorelbine/cisplatin alone; monitoring would have included radiologic evaluations every second cycle.

Number of patients:
Planned:
Part 1 – Dose Escalation: up to 18 patients (based on number of patients required to determine MTD)
Part 2 – Randomised Treatment: 118 patients (1:1 randomisation to L-DOS47 in combination with vinorelbine/cisplatin or vinorelbine/cisplatin alone)

Analyzed:
Part 1 – 9 patients
Part 2 – Not applicable as study was early terminated in Part 1.

Diagnosis and main criteria for inclusion:
Adults with histologically confirmed metastatic lung adenocarcinoma, Grade 1 – 4; Eastern Cooperative Oncology Group (ECOG) performance status 0 – 1; life expectancy ≥ 3 months; chemo-naive or not prior adjuvant chemotherapy within 6 months of first treatment day if there is recurrent disease; at least a single measurable lesion in accordance with RECIST v1.1; not receiving radiotherapy, targeted therapy, hormonal therapy, immunotherapy, major surgery or other study drugs during the 4 weeks prior to study treatment

Test product dose, mode of administration, batch numbers:
L-DOS47 was administered as a 30-minute IV infusion, on Days 1 and 8 of each treatment cycle, followed by vinorelbine IV infusion on Days 2 and 9 over 6 to 10 minutes and cisplatin IV infusion on Day 9 (only) over 60 minutes. Dosing during Part I (dose escalation phase) increased for successive cohorts from 6, 9 and 12 μg/kg. In Part II, all patients were to have received the selected dose determined in Part I. The following L-DOS47 batches were used in the study: 2128-103.

Duration of treatment:
The maximum duration of the study was approximately 16 weeks (including up to 21 days for Screening, up to 4 cycles of treatment and an End-of-Treatment Visit after the last 21-day treatment cycle).

Follow-up for disease progression was conducted by radiologic assessments every 6 weeks (± 7 days) until one of the following occurred: disease progression, patient initiated non-study cancer treatment, patient withdrew consent, or became lost-to-follow-up. Survival data was captured by telephone call every 30 days (± 7 days) and patients were to be followed until death, or until the study is terminated.

Reference therapy:
In Part II (randomized treatment), the planned control arm was vinorelbine plus cisplatin alone.

Criteria for evaluation:
Safety
Safety was assessed by reported AEs, serious adverse events (SAEs), vital signs (respiratory rate, heart rate, body temperature, blood pressure, and oxygen saturation [pulse oximetry]), ECOG performance status, clinical laboratory evaluations (haematology, chemistry, coagulation, and urinalysis), anti-L-DOS47 antibody levels, and 12-lead electrocardiograms (ECGs). Blood samples were also collected for measurement of L-DOS47 peak and trough concentrations.

Efficacy
Efficacy was to be assessed by:

- Time to Progression, as defined as the time from randomisation until objective tumour progression.
- Objective response, as assessed according to the RECIST v1.1 criteria.
- Overall survival (time to death), as defined as the time from the first day of study drug administration to death due to any cause.

Statistical methods:
Primary Endpoint
The primary endpoint was time to disease progression.

Secondary Endpoints
Secondary endpoints included:

- Objective response as measured using RECIST v. 1.1, defined as the proportion of patients with a best overall response of complete response and partial response.
- Overall survival
- Safety and tolerability of L-DOS47 in combination with vinorelbine/cisplatin

General

Due to the early termination of the study protocol with only nine subjects enrolled in the dose escalation part of the study (Part 1), only a very limited analysis is reported.

Disposition of patients was summarized in terms of entering and completing each phase of the study, as well as any patients discontinuing early and reasons for discontinuation.

There were two defined populations:

Safety Evaluable:	Comprises all subjects who receive at least one study drug dose (partial or complete). The safety population is the basis for safety summaries.
Response Evaluable:	Consists of all subjects who enrol in the study and receive at least one study drug dose (partial or complete) and have at least one post-baseline response assessment.

Demographic data was summarized by means of descriptive statistics (n, mean, median, minimum, maximum).

Treatment exposure, including dosing information and compliance was summarized by means of descriptive statististics (n, mean, median, minimum, maximum).

Efficacy Analyses

Data from all sites and dosing cohorts was combined. Time to event data (i.e., TTP and OS) was analysed using Kaplan-Meier survival estimates.

A summary of Best Objective Response Rate (BORR) including all response evaluable patients was completed, where BORR is defined as:

$$BORR = (CR + PR)/Nr$$

where CR is the number of patients with complete response, PR is the number of patients with partial response, and Nr is the number of patients that are included in the Response Evaluable Population.

Tumour response evaluation was performed using the RECIST v1.1 definitions. Additionally, all ECOG performance status scores were tabulated for all patients.

Safety Analyses

All AEs recorded during the study were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) system (MedDRA 21.1) and assigned to a System Organ Class (SOC). Treatment-emergent AEs (TEAEs) was defined as AEs that first occurred or worsened

in severity after initiation of therapy. For any given MedDRA preferred term (PT), a patient contributed a single count to the incidence, even if the patient had multiple occurrences over multiple courses of treatment. Relationship to study treatment was classified as related (definitely, probably, or possibly) and unrelated (unlikely, unrelated). If multiple records existed for 1 patient, only maximum severity and strongest relationship to study treatment was counted for calculating percentage.

A summary of all TEAEs by SOC, toxicity grade and relatedness to any component of the study treatment regimen was tabulated. A frequency tabulation of all TEAEs summarized by SOC, PT, toxicity grade, and dosing cohort was also summarized for all patients who received any amount of treatment. Similarly, tabulations of all L-DOS47-related TEAEs as well as any SAEs, by SOC, toxicity grade and dosing cohort was also included.

Clinical laboratory, ECG, and vital sign parameters were evaluated for out of normal range assessments. Clinically significant abnormalities were noted and summarized.

Extent of L-DOS47 exposure was be tabulated by number of cycles, total duration, total planned and administered dose, overall compliance, and summarized by descriptive statistics (i.e., mean, standard deviation [StatD], median, minimum, and maximum values).

Exploratory Analyses
Plasma L-DOS47 concentrations and immunogenicity data were not reported due to incomplete shipment of samples to the central laboratory and the inability to complete sample reconciliation against recorded collection dates.

Summary:
Efficacy Results
Of eight patients who were deemed efficacy evaluable, two patients (25%) had PR, four patients (50.0%) had SD, and two patients (25.0%) had PD. The ORR (CR + PR) was 25%. The clinical benefit rate was (CR + PR + SD) was 75%. The calculated median time to progression was 169.5 days. The calculated median survival time was 275 days. However, four of nine patients were censored due to premature conclusion of the survival follow-up period.

Safety Results
Overall, nine patients were exposed to L-DOS47 dose ranging from 6 to 12 μg/kg in combination with cisplatin and vinorelbine. All nine patients (100%) reported at least one TEAE of any severity grade, although the majority were of mild to moderate grade. The most common TEAEs were blood and lymphatic system disorders, reported in all nine patients (100%), including anaemia in five patients (55.6%), leukopenia in 6 patients (66.7%), and neutropenia in seven patients (77.8%). Next most common were gastrointestinal disorders, reported in seven patients, most notably nausea, which was reported in seven patients (77.8%). No trends were observed between frequency of TEAEs, toxicity grade and escalating L-DOS47 dose levels.

No DLTs were reported in this study and the only SAE reported, acute stress disorder, was assessed as unrelated to study treatment. While there were some observed trends with decreases

in haemoglobin, as well as lowered white cell and neutrophil counts, this is not unexpected in this patient population who was also receiving cisplatin-based chemotherapy.

Analysis of plasma L-DOS47 levels and serum anti-L-DOS47 antibody levels could not be completed as per the original plan due to the early study termination and incomplete samples reconciliation and delivery to the central laboratory. However, given the limited patient enrolment, their analyses would have very limited utility.

Conclusions:
Due to the extenuating circumstances surrounding the early termination of the trial because of the global pandemic restrictions followed by the war in Ukraine, the original study objectives could not be met. Nevertheless, L-DOS47 was administered at doses ranging from 6 to 12 μg/kg in combination with cisplatin and vinorelbine to nine patients with metastatic lung adenocarcinoma, who were classified as either chemo-naïve or recurrent following surgery with no adjuvant chemotherapy in prior six months, and was found to:

- Be reasonably well-tolerated as eight of nine patients were able to complete all four treatment cycles as per protocol. Only one patient discontinued as a result of an unrelated SAE (acute stress disorder) and was no longer able to continue consenting to be in the study.
- Be associated with L-DOS47-related TEAEs ≤ Grade 2, mostly of the mild variety and resolved during the treatment period.
- While the numbers of patients enrolled did not permit drawing any significant conclusions on efficacy, of eight response evaluable patients, PR was observed in two patients (25.0%), SD was reported in four patients (50.0%). The ORR (CR+PR) was 25.0%, with median TTP of 169.5 days and clinical benefit (CR+PR+SD) of 75.0%.