Phase I/II dose escalation study of L-DOS47 as a monotherapy in non-squamous non-small cell lung cancer patients

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Introduction

It has been observed that human solid tumours produce an acidic local microenvironment. This metabolic condition can induce metastasis and confer a growth advantage to certain cancers. Helix BioPharma Corp. (Helix) has developed an immunoconjugate cancer therapeutic to exploit the acidic tumour extracellular environment. The molecule, L-DOS47, is a protein conjugate consisting of jack bean urease conjugated to a llama monoclonal antibody (AFAIKL2) that is targeted to the carcinoembryonic antigen-related cell adhesion molecule 6 (CEACAM6) antigenic tumour marker. CEACAM6 is a glycosylphosphatidylinositol (GPI)-anchored cell adhesion molecule that is overexpressed in many cancers is associated with adhesion and invasion. The AFAIKL2 antibody serves as a targeting agent to deliver the enzyme to the affected sites while the urease enzyme converts urea, an abundant metabolite, into ammonia and generates a local pH increase. The combined effect of ammonia toxicity and pH increase is cytotoxic to cancer cells in culture and in xenograft models.

This is a Phase I/II, open-label, non-randomised study designed to evaluate the safety and tolerability of ascending doses of study drug (L-DOS47) in male and female patients aged ≥ 18 years old with Stage IIIb or IV non-squamous non-small cell lung cancer (NSCLC). The staging of NSCLC was conducted according to Tumour Node Metastases (TNM), 7th Edition. Patients were recruited into cohorts, with a minimum of three and a maximum of six patients per cohort. The starting dose of L-DOS47 for the first cohort was 0.12 µg/kg; further dose levels assessed were 0.21, 0.33, 0.46, 0.59, 0.78, 1.04, 1.38, 1.84, 2.45, 3.26, 4.33, 5.76, 7.66, 10.19 and 13.55µg/kg.

Primary objectives:

i) To define the maximum tolerated doses of multiple doses of L-DOS47;
ii) To make a preliminary assessment of the efficacy of L-DOS47.

Secondary objectives:

i) To evaluate the pharmacokinetics and immunogenicity of L-DOS47;
ii) To evaluate the safety and tolerability of multiple doses of L-DOS47.

Acknowledgements

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HELIX BIOPHARMA

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Table 1: Patient Disposition

Patient Disposition	Total
Screened	90
Screen Failures	35
Treated	55
Completed 4 Cycles	21
Additional Cycles	16
Ongoing	1
Withdrawn	34

Patient disposition is summarized in **Table 1**. A total of ninety (90) patients were consented and screened for participation in the study. Of the 90 screened patients, fifty-five (55) patients were administered at least one dose of L-DOS47 at dose levels ranging from 0.12 to 13.55µg/kg. Twenty-one (21) patients completed four treatment cycles and sixteen (16) patients were administered additional L-DOS47 cycles. At the time of this report, one (1) patient in cohorts 15 (10.19µg/kg) was ongoing. As expected, the primary reason for patient discontinuation was **progression of NSCLC**. Radiological disease progression was assessed as per RECIST criteria v1.1.

Table 2: Patient Demographics

Patient Demographics	Total N = 55
Age	**Mean = 60.9** **Min, Max (34, 83)**
Weight (kg)	**N = 55** **Mean = 68.4** **Min, Max (48, 95)**
Gender Male Female	 ***N = 29 (53%)*** ***N = 26 (47%)***
Race Caucasian	 ***N = 55 (100%)***
Stage IIIB IV	 ***N = 7 (13%)*** ***N = 48 (87%)***
ECOG 0 1 2	 ***N = 13 (24%)*** ***N = 40 (73%)*** ***N = 2 (3%)***

Table 3: Prior Cancer Therapies

Prior Cancer Therapies	Total (n=55)
Prior Therapy	***None = 8 (16%)*** ***Chemo/Target = 47 (85%)*** ***Radiation = 26 (47%)*** ***Surgery = 17 (31%)***
Prior Chemo/Target Therapy	***Adjuvant = 4 (7%)*** ***Locally Advanced = 3 (5%)*** ***Metastatic Disease = 37 (67%)*** ***Palliative = 3 (5%)*** ***Unknown = 4 (7%)***
Best Response	***Unknown = 4 (8%)*** ***CR = 1 (2%)*** ***PR = 14 (30%)*** ***Stable = 20 (43%)*** ***PD = 8 (17%)***

Tables 2 and 3 summarize Patient Demographics and Prior Cancer Therapies. Fifty-three (53) or 97% had a baseline ECOG performance status of 0 (Fully active, able to carry on all pre-disease performance without restriction) or 1 (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work).

Forty-eight (48) or 87% of patients were Stage IV as assessed according to TNM, 7th edition and based on computed tomography (CT) scan. None of the patients had prior history of other malignancies or had a known history of central nervous system metastatic disease.

Of the 390 doses administered to patients in the Phase I study, 96% were administered without a dose delay or dose interruption. Comparatively, patients in cohorts 13 to 16 (5.76 to 13.55µg/kg) were exposed to more L-DOS47 for a longer duration without a significant change to the safety profile of L-DOS47 compared to the other dosing cohorts. At the time of this report, one (1) patient in cohort 15 continues to receive additional cycles of L-DOS47.

Table 4: Treatment Emergent Adverse Events (>5%)

System Organ Class Preferred Term	Toxicity Grade (No. of pts) 1	2	3	4	5	No. of pts N=55	(%) pts
Blood and Lymphatic System Disorders							
Anemia		1	4			5	9%
						5	9%
Gastrointestinal Disorder						11	20%
Abdominal pain	2	1				3	5%
Nausea	3	5				8	16%
Vomiting	4		1			5	9%
General Disorder and Admin Site Cond						20	36%
Asthenia	2	2	1			5	9%
Edema Peripheral	1	2				3	5%
Fatigue	4	3				7	13%
General physical health deterioration		2		1	1	4	7%
Non-cardiac chest pain	2	1				3	5%
Infections and infestations						7	13%
Pneumonia		2	2			4	7%
Metabolism and Nutritional Disorder						7	13%
Decreased Appetite	1	4				5	9%
Musculoskeletal and connective tissue						8	16%
Bone pain		2		1		3	5%
Neoplasms benign, malignant						7	13%
Non-small cell lung cancer				1	4	5	9%
Psychiatric disorders						8	16%
Insomnia	3	3				6	11%
Respiratory, thoracic and mediastinal						21	38%
Cough	4	2				6	11%
Dyspnea	4	7	1	2	1	15	27%

Table 4 summarizes treatment emergent adverse events reported in the Phase I component of study LDOS002. Forty-four (44), or 80% of the patients in the safety population had at least one treatment emergent adverse events.

The most common adverse event reported by 15 or 27% of patients was **dyspnea**. This is consistent with what is expected for the disease under study and expected from what was reported from animal toxicity studies. Also consistent with what was reported pre-clinically were gastrointestinal disorders like **vomiting** and **nausea**, general disorders like **asthenia** and **fatigue** and metabolic and nutritional disorders like **decreased appetite**.

Patients experienced infusional reactions **chills**, **dyspnea** and **infusion site pain and pruritus**; however, these events were low grade and resulted in a temporary discontinuation of L-DOS47.

Unexpected adverse events reported deemed related to L-DOS47 by the site investigators with and incidence of greater than or equal to 5% included **anemia** and **bone pain**. Low grade adverse events deemed related to L-DOS47 by the site investigators with an incidence of less than 5% include **atrioventricular block**, **atrioventricular block first degree** and **dermatitis exfoliative**.

The only DLT reported in Phase I was a grade 4 **bone pain** resulting in the permanent discontinuation of L-DOS47. The event stopped following a de-challenge of L-DOS47. **Bone pain** was observed in 5% of patient, mostly in the later L-DOS47 dosing cohorts and should be considered a potential risk to patients in subsequent studies.

L-DOS47 did not elicit a dose-dependent release of cytokines at doses up to 13.55µg/kg.

Figure 1: Plasma L-DOS47 Concentration-time Curve

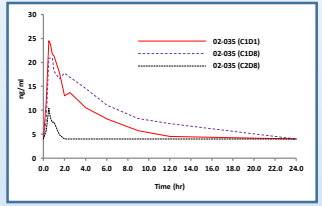

Figure 2: Dose Response Relationship

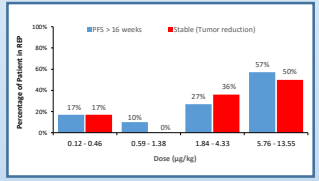

Figure 3: Kaplan Meier Plot

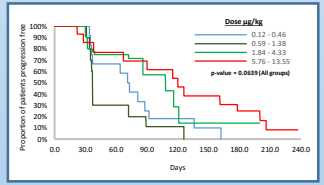

Figure 1 is a representative plasma L-DOS47 concentration time curve for patient **02-035** during Cycle 1, Days 1 and 8 (C1D1, C1D8) and Cycle 2 Day 8 (C2D8). Tmax was consistent across dose levels and treatment cycles occurring within the first hour following the start L-DOS47 infusion. A dose proportional increase in both Cmax and $AUC_{(0\text{-}t)}$ was observed during the C1D1 dosing across dose levels. A decrease in the $AUC_{(0\text{-}t)}$ was observed in most patients following the C2D8 dosing for all dose levels where pharmacokinetic data is available. This is consistent with production of anti-L-DOS47 antibodies. The mean half-life of L-DOS47 for doses administered to-date range from 2.38 to 10.9 hours.

Figure 2 summarizes the biologic activity and potential clinical benefit of L-DOS47 in the response evaluable population at dose ranges 0.12 - 0.46, 0.59 - 1.38, 1.84 - 4.33 and 5.76 - 13.55µg/kg. The response evaluable population includes: all patients that had measurable disease at baseline; received at least one dose of L-DOS47; and had at least one post-baseline response assessment . Forty-seven (47) of the 55 patient dosed in the Phase I component of the study contributed to the response evaluable population.

A dose response trend was observed when comparing the percentage of patients who were progression free at 16 weeks across dose ranges. A similar trend was observed when comparing the percentage of patient who had Stable Disease (as defined in RECIST v1.1) and had a reduction in target lesions.

Figure 3 is a Kaplan Meier plot of patients in the response evaluable population that were progression free during the L-DOS47 treatment period by dosing group. Progression free survival (PFS) is defined as the length of time during and after treatment in which a patient is living with a disease that does not get worse. PFS was computed as the elapsed time between study Day 1 and the first date of progression as determined by the Investigator or death (any cause). Patients not experiencing disease progression and who did not die while on treatment had their event time censored on the last study date that verified lack of disease progression.

Conclusion:

The MTD of L-DOS47 was not reached in the Phase I component of study LDOS002 at doses administered up to 13.55µg/kg. One (1) AE, **bone pain** in cohort 13 (5.76µg/kg) met the DLT criteria defined in the protocol resulting in the expansion of the dosing cohort. AE and PK data from the Phase I study validated observations reported from the preclinical research supporting the first-in-man study. Since this was a first in man study, particular attention was given to events observed in preclinical toxicology studies. L-DOS47 was well tolerated at all dose levels up to 13.55µg/kg.

Following the review of clinical data collected to-date, L-DOS47 is near achieving many of the goals of early phase study; namely to determine the initial safety profile of the product and to acquire enough data to defend a proposed dose with which to subsequently test in various cancer indications. These data also suggest that L-DOS47 may be effective in treatment of CEACAM6 expressing tumors and may be more efficacious in combination with other therapies that may benefit from the pH-modulating effects of L-DOS47.