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

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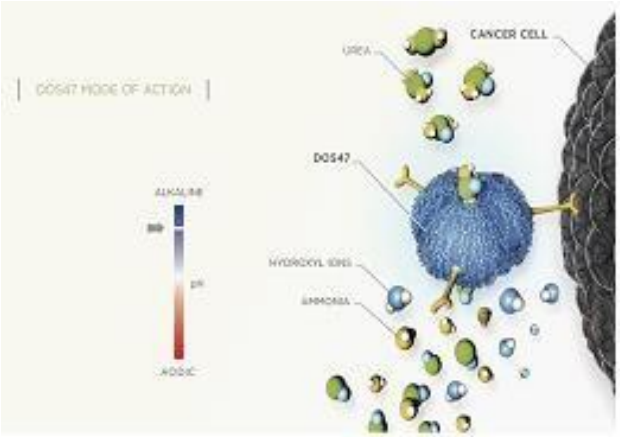
Disclosure of Relevant Financial Relationships:

I am a full-time employee of Helix BioPharma Corp.

L-DOS47



- L-DOS47 is a camelid-antibody-urease conjugate that targets ceacam6 expressing adenocarcinoma cells
- L-DOS47 converts urea into ammonia which is cytotoxic to cancer cells. It also raises local pH to enhance the action of certain chemotherapeutics
- L-DOS47 is efficacious in lung and pancreatic preclinical cancer models

- L-DOS47 has been examined in rodent and primate preclinical toxicology models including effects on cytokine release and immunogenicity
- L-DOS47 is prepared in a stable lyophilized dosage form and is delivered through intravenous infusion

Objectives: **Primary objectives:**

Phase I: To define the maximum tolerated doses of multiple doses of L-DOS47

Phase II: To make a preliminary assessment of the efficacy of L-DOS47

Secondary objectives:

- To evaluate the pharmacokinetics and immunogenicity of L-DOS47
- To evaluate the safety and tolerability of multiple doses of L-DOS47

Design:

- Phase I/II, open-label, non-randomised, 3+3, study to evaluate the safety and tolerability of ascending doses of L-DOS47 in patients aged ≥ 18 years old with inoperable, locally advanced, recurrent or metastatic Stage IIIb or IV non-squamous NSCLC.
- L-DOS47 is administered i.v. weekly over 14 days followed by 7 days rest (one treatment cycle is 3 weeks).
- All patients (Phase I and II) receive up to four cycles of L-DOS47
- Patients continue to receive L-DOS47 as long as there is sustained clinical benefit and it is well tolerated.
- The decision for dose escalation is made by the Trial Steering Committee (TSC).
- A DLT is defined as any NCI CTCAE v4.0 ≥ Grade 3 non-hematologic and any ≥ Grade 4 hematologic AE that is at least possibly related to L-DOS47 occurring ≤ 3 weeks after commencing L-DOS47 treatment.
- In Phase II, the decision rules based on an optimal Simon two-stage.

Doses of 0.12, 0.21, 0.33, 0.46, 0.59, 0.78, 1.04, 1.38, 1.84, 2.45, 3.26, 4.33 and 5.76 micrograms of L-DOS47 per kilogram of patient body weight have been successfully administered to study patients.

Study Status	Total
Patients Screened	*75*
Screen Failures	*32*
Patients Treated	*43*
Patients Ongoing (Cohorts 12 & 13)	*3*
Patients Completing 4 Cycles of Therapy	*14*
Patient Withdrawals	*26*

Demography and NSCLC Baseline Characteristics (Cohort 1 to 12)

Demography	Total (N=40)	NSCLC History	Total (N=40)
Age	*Mean = 61.2* *Min, Max (34, 83)*	Tumor Histology	*Adeno = 38 (95%)* *Large Cell = 1 (2.5%)* *Unknown = 1 (2.5%)*
Weight (kg)	*Mean = 69.1* *Min, Max (48, 95)*	Tumor Staging	*Stage IIIB = 7 (17.5%)* *Stage IV = 33 (82.5%)*
Gender Male Female	 *21 (52.5%)* *19 (47.5%)*	Prior Therapy	*None = 8 (20%)* *Chemo/Target = 32 (80%)* *Radiation = 21 (52.5%)* *Surgery = 11 (27.5%)*
Race Caucasian	*40 (100%)*	Prior Chemo/Target Therapy	*Adjuvant = 2 (5%) Locally Advanced = 3 (7.5%) Metastatic Disease = 31 (77.5%) None = 9 (22.5%)*
ECOG 0 1 2	 *11 (27.5%)* *27 (67.5%)* *2 (5%)*	Best Response	*Unknown = 5 (16.1%)* *CR = 1 (3.2%) PR = 9 (29%) Stable = 9 (29%) PD = 7 (22.6%)*

Treatment Related Adverse Events (Cohort 1 to 12)

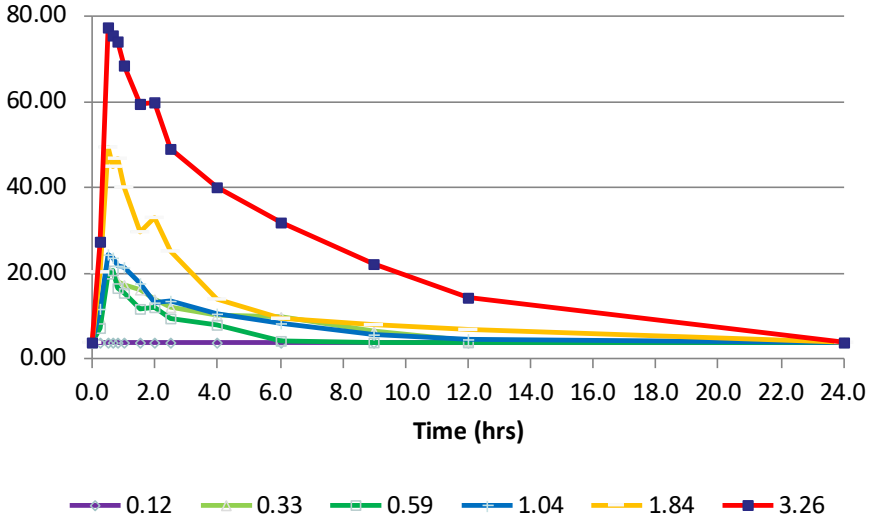
(8 patients or 20% of patients in the first 12 cohorts reported events that were considered related to the investigational pr oduct)

System Organ Class Preferred Term	Grade	No. of patients (N = 40)	% of patients
Blood and lymphatic system disorders		1	2.5%
Anemia	**3**	1	2.5%
Cardiac Disorders		2	5%
Atrioventricular block	**1**	1	2.5%
Atrioventricular block first degree	**1**	1	2.5%
Gastrointestinal Disorders		2	5%
Nausea	**2**	2	5%
Vomiting	**1**	1	2.5%
General disorders and administration site conditions		3	7.5%
Chills	**1**	1	2.5%
Fatigue	**1, 2**	1	2.5%
Injection Site Reactions	**1**	1	2.5%
Metabolism and Nutritional Disorders		1	2.5%
Loss of Appetite	**1, 2**	1	2.5%
Respiratory, thoracic and mediastinal disorders		2	5%
Dyspnea	**1, 2**	2	5%

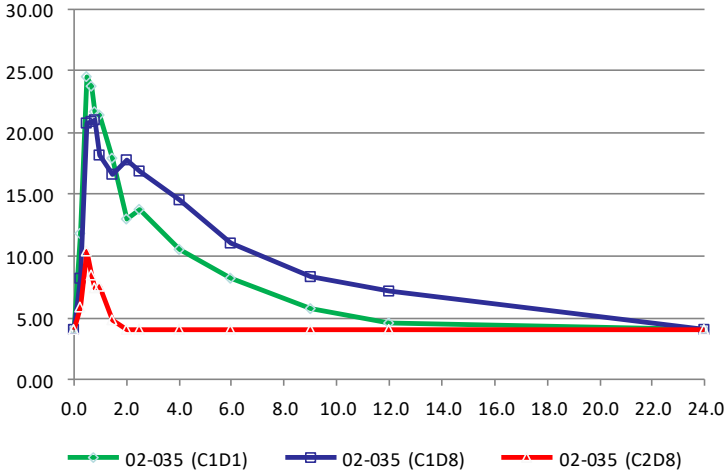
DLT reported in cohort 13 – Grade 4 Back Pain

- Cytokine panel: IL-1β, IL-IRA, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IFN gamma-induced protein (IP)-10, IFN-α, IFN-γ, TNFα, GM-CSF, G-CSF
- 14 cytokines for 40 patients analyzed to-date
- No evidence that L-DOS47 elicits a dose-dependent release of cytokines in the first 12 dosing cohorts
- Brief increases in IL-6 observed in a few patients consistent with what was observed in the repeat-dose monkey tox study.
- Cannot determine at this time whether changes in various cytokine levels were directly related to L-DOS47.
- Tmax was consistent across dose levels and treatment cycles occurring within the first hour following the start L-DOS47 infusion.
- A decrease in the $AUC_{(0\text{-}t)}$ was observed following the C2D8 dosing for all dose levels where PK data is available. This is consistent with production of anti-L-DOS47 antibodies.
- Immunogenicity analysis following repeat dosing of monkeys with L-DOS47 indicated the presence of anti-drug antibodies by Day 14, and these were correlated with decreased exposure to L-DOS47 as determined by TK analysis.

Graph 1: ***Plasma Concentration vs. Time (Representative Patient)***



Graph 2: ***Plasma Concentration vs. Time 1.04 µg/kg (Cohort 7)***



ADA Positive ***C1D8(-), C2D1(-), EOT(+), FUP(+)***

- 21/40 patients had an overall response of SD at cycle 2
- 10/40 patients had an overall response of SD at cycle 4
- Patient 01-047 enrolled in cohort 9 (1.84µg/kg) was progression free for 10 cycles (approx. 7 months)
- None of the patients treated to-date have had a partial or complete response as defined by RECIST v1.1 definition.
- The Trial Steering Committee has approved enrollment of patient to cohort 13 (5.76µg/kg).
- One DLT reported in cohort 13 (Grade 4 Back Pain)
- The protocol is approved for enrollment of patients to cohort 16 (13.55µg/kg).
- Phase Ib combination study with pemetrexed carboplatin currently enrolling in the U.S.
- Phase II combination study with vinorelbine cisplatin planned

- No safety issues beyond those observed in pre-clinical toxicology studies or expected in the population of patients being studied.
- Continue to closely follow cardiovascular events (AV block)
- One Dose Limiting Toxicities reported to-date (cohort 13: back pain)
- Phase II dose to be determined
- Pharmacokinetic data supports continued dose escalation
- Immunogenicity consistent with what was observed pre-clinically
- Clinical trends observed to-date are encouraging