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 I/II Open-Label, Non-Randomized Dose Escalation Study of Immunoconjugate L-DOS47 as a Monotherapy in Non-Squamous Non-Small Cell Lung Cancer Patients</td></tr>
<tr><td colspan="3">Investigators: Dariusz M. Kowalski, MD, PhD; Maciej Krzakowski, MD, PhD; Cezary Szczylik, MD, PhD; Prof. Elżbieta Wiatr, MD, PhD; Aleksandra Szczesna, MD, PhD; Rodryg Ramlau, MD, PhD</td></tr>
<tr><td colspan="3">Study centres: Maria Sklodowska-Curie Memorial Cancer Centre and Institute, Warsaw and four other centres in Poland.</td></tr>
<tr><td colspan="3">Publication: Data reported in part in Ramlau et al. J Thoracic Oncol 2017;12 (Suppl 1): S1071–S1072.</td></tr>
<tr><td colspan="3">Studied period (years):
Date of first enrolment (Phase I): 9 October 2012
Date of last patient visit (Phase II): 1 August 2017</td></tr>
<tr><td colspan="3">Phase of development: I/II</td></tr>
<tr><td colspan="3">Objectives:
Primary objectives:
Phase I:
• To define the maximum tolerated dose (MTD) of multiple doses of L-DOS47 administered intravenously to patients with non-squamous non-small cell lung cancer (NSCLC) when given as a monotherapy, where the MTD is defined as the highest dose level at which ≤2 dose limiting toxicities are observed in patients in a dosing cohort ≤3 weeks after commencing L-DOS47 treatment
Phase II:
• To assess the preliminary efficacy of L-DOS47 in patients with NSCLC
Secondary objectives:
Phase I and II:
• To evaluate the pharmacokinetics (PK) of L-DOS47 in patients with NSCLC
• To evaluate the immunogenicity of L-DOS47 in patients with NSCLC
• To evaluate the safety and tolerability of multiple doses of L-DOS47 in patients with NSCLC</td></tr>
<tr><td colspan="3">Methodology:
Phase I/II, open-label, non-randomized 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 NSCLC.</td></tr>
</table>

- In *Phase I,* L-DOS47 was administered weekly over 14 days followed by 7 days rest (one treatment cycle was 3 weeks)
- In *Phase II,* L-DOS47 was administered twice weekly over 14 days (Day 1, 4, 8 and 11) followed by a seven-day rest

Number of patients:
Planned:
- *Phase I,* 90 patients enrolled (no formal power calculation)
- *Phase II,* 39 patients, based on power calculation. Enrolment was required to stop after pre-specified safety and preliminary efficacy analysis of first 17 patients

Analyzed:
- *Phase I,* 55 patients
- *Phase II,* 21 patients

Diagnosis and main criteria for inclusion:
Adults with histologically confirmed Stage IIIb or IV NSCLC; Eastern Cooperative Oncology Group (ECOG) performance status 0–2; life expectancy ≥3 months. Not receiving radiotherapy (except symptomatic treatment of bone metastases), targeted therapy, hormonal therapy or immunotherapy, major surgery or other study drugs within prior 4 weeks.

Test product dose, mode of administration, batch numbers:
L-DOS47 was administered as a 30-minute IV infusion on a pre-specified schedule (weekly in Phase I, twice weekly in Phase II). Dosing in Phase I increased for successive cohorts, from 0.12 μg/kg to 13.55 μg/kg L-DOS47. In Phase II, all patients received 13.55 μg/kg L-DOS47. The following L-DOS47 batches were used in the study: 2128-101, 2128-102 and 2128-103.

Duration of treatment: Approximately 20 weeks, including up to 21 days for screening; up to four cycles of treatment; End-of-Treatment Visit (EOTV), 7 days after the last dose; and follow-up visit 30 days after the last dose; survival follow-up every 30 days thereafter. Some patients had the option to continue additional treatment cycles as long as there was sustained clinical benefit and treatment was well tolerated.

Reference therapy: None; open-label, single-arm, non-randomized study.

Criteria for evaluation:
<u>Efficacy</u>
Primary endpoint *(Phase II)*:
- Overall response rate (ORR) defined as proportion of patients with a best (confirmed) objective response of complete response (CR) and partial response (PR), as assessed according to Response Evaluation Criteria in Solid Tumour (RECIST) v1.1. Secondary efficacy endpoints include time to disease progression (TTP), progression-free survival (PFS) and overall survival (OS)

<u>Safety</u>
Primary endpoint (Phase I):
- Incidence and severity of drug-related adverse events (AEs)

Phase I and II secondary endpoints:
- L-DOS47-related toxicity during the first 2 hours after infusion, as assessed by:
  - Incidence and severity of AEs, serious adverse events (SAEs)
  - Change in vital signs
- Incidence and severity of AEs, SAEs
- Evaluation of L-DOS47 pharmacokinetics over time

- Evaluation of anti-L-DOS47 antibodies over time

Statistical methods:

Descriptive statistics for the safety and efficacy variables: Continuous variables are summarized by mean, standard deviation, minimum, median and maximum; categorical variables are summarized by frequency counts and percentages. PK parameters were determined from L-DOS47 concentrations using non-compartmental methods (WinNonlin®).

Summary:

Efficacy results (evaluated in *Phase II* only):

No complete or partial responses were identified in the Per Protocol (PP; n=5) or Response Evaluable (RE; n=19) Populations. One patient (20%) in the PP Population and 4 (21%) in the RE Population experienced stable disease (SD) by the end of the treatment period. Median time to progression and median OS were 151 days and not reached, respectively, in the PP Population; and 56 and 191 days, respectively, in the RE Population.

Safety results:

In *Phase I*, the MTD of L-DOS47 was not reached for doses administered up to 13.55 μg/kg, with a single dose-limiting toxicity (DLT), (bone pain) reported for the 5.76 μg/kg cohort. No significant unexpected toxicity was observed in the first 2 hours after infusion. Other than a trend toward a transient decrease in blood pressure (BP) and/or heart rate (HR) soon after L-DOS47 administration in both *Phase I* and *Phase II* patients, no trends were observed related to vital signs, physical examination, weight, electrocardiogram (ECG) findings or clinical laboratory values.

In *Phase I*, the most common class of treatment-emergent adverse events (TEAEs), reported by 27% of patients, was respiratory/thoracic/mediastinal disorders including dyspnea. SAEs considered possibly drug-related included one episode of Grade 3 anemia and one episode of Grade 4 bone pain. In Phase II, the most common class of TEAEs, reported by 53% of patients, was gastrointestinal disorders including nausea and vomiting. SAEs considered possibly drug related included one episode of Grade 3 dyspnea and one episode of Grade 3 spinal pain.

Upon initial dosing, systemic exposure tended to increase with increasing L-DOS47 dose, but there was no apparent correlation between dose and plasma half-life. Upon repeat dosing for both *Phase I* and *Phase II*, systemic exposure was variable and substantially decreased in most cases, possibly due to the development of anti-L-DOS47 antibodies, which were seen in almost all patients. Conversely, circulating tumour antigen carcinoembryonic antigen-related cell adhesion molecule 6 (CEACAM6) levels did not appear to affect L-DOS47 exposure. While minor transient increases in cytokines interleukin (IL)-6, IL-8 and interferon gamma-induced protein (IP)-10 were observed in a few patients, there was no evidence that L-DOS47 elicits dose-dependent cytokine release.

Conclusions:

L-DOS47 was generally well tolerated at weekly doses of 13.55 μg/kg (*Phase I*) and twice-weekly doses of 13.55 μg/kg (*Phase II*). Used as monotherapy in patients with advanced NSCLC, L-DOS47 treatment did not lead to complete or partial treatment response in any patients in *Phase II*.