PROTOCOL

A Phase I, Open Label, Dose Escalation Study of Immunoconjugate L-DOS47 in Combination with Standard Doublet Therapy of Pemetrexed/Carboplatin in Patients with Stage IV (TNM M1a and M1b) Recurrent or Metastatic Non-Squamous Non-Small Cell Lung Cancer

Helix Protocol No.:	LDOS001
Theradex Protocol No.:	H13-11042
IND No.:	105544
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Medical Monitor:	Theradex® 4365 Route 1 South Suite 101 Princeton, New Jersey 08540 (609) 799-7580
Date:	**August 10, 2017**

INVESTIGATOR'S STATEMENT

1. I have carefully read this protocol entitled "A Phase I, Open Label, Dose Escalation Study of Immunoconjugate L-DOS47 in Combination with Standard Doublet Therapy of Pemetrexed/Carboplatin in Patients with Stage IV (TNM M1a and M1b) Recurrent or Metastatic Non-Squamous Non-Small Cell Lung Cancer" and agree that it contains all the necessary information required to conduct the study. I agree to conduct this study as outlined in the protocol.

2. I understand that this study will not be initiated without approval of the appropriate Institutional Review Committee/Independent Ethics Committee (IRB/IEC), and that all administrative requirements of the governing body of the Institution will be complied with fully.

3. Informed written consent will be obtained from all participating patients in accordance with institutional guidelines, FDA requirements as specified in Title 21 CFR, Part 50, the European Union Directive 2001/20/EC and its associated Detailed Guidances, European Union GCP Directive 2005/28/EC, the ICH Guideline for Good Clinical Practice, Section 4.8, and the terms of the Declaration of Helsinki (2013).

4. I will enroll patients who meet the protocol criteria for entry.

5. I understand that my signature on each completed Case Report Form indicates that I have carefully reviewed each page and accept full responsibility for the contents thereof.

6. I understand that the information presented in this study protocol is confidential, and I hereby assure that no information based on the conduct of the study will be released without prior consent from the Sponsor unless this requirement is superseded by the Food and Drug Administration, a Competent Authority of the European Union or another Regulatory Authority.

Investigator:
Name: _____ Telephone: _____

Address: _____

_____

_____

Signature: _____ Date: _____

Sponsor Representative:
Signature: _____ Date: 15 AUG 2017

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CLINICAL STUDY SYNOPSIS

Name of Sponsor: Helix BioPharma Corp **21 St. Clair Avenue East** **Suite 1100** **Toronto, ON M4T 1L9** **Canada** **(416) 925 3232 (phone)**	**Name of Monitor:** Theradex® 4365 Route 1 South Suite 101 Princeton, NJ 08540 (609) 799-7580 (phone) (609) 799-4148 (fax)

Name of finished product: L-DOS47

Name of active ingredient: L-DOS47 is an immunoconjugate drug composed of single chain antibody molecules specific for carcinoembryonic antigen-related cell adhesion molecule 6 (CEACAM6), cross-linked with a purified urease derived from the Jack-Bean plant.

Title of the study:
A Phase I, Open Label, Dose Escalation Study of Immunoconjugate L-DOS47 in Combination with Standard Doublet Therapy of Pemetrexed/Carboplatin in Patients with Stage IV (TNM M1a and M1b) Recurrent or Metastatic Non-Squamous Non-Small Cell Lung Cancer

Investigators and study centers:

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Publication (reference):

Not applicable

Clinical phase: Phase I

Objectives:
Primary Objectives:

- Safety and tolerability of L-DOS47 in combination treatment with pemetrexed/carboplatin
- Determination of dose limiting toxicity of L-DOS47 in combination treatment with pemetrexed/carboplatin
- Determination of maximum tolerated dose (MTD) and recommended Phase II dose of L-DOS47 in combination treatment with pemetrexed/carboplatin

Secondary Objectives:

- Objective response rate of the combination treatment according to RECIST 1.1
- Evaluation of clinical benefit, defined as the percentage of patients who have achieved complete response, partial response, and stable disease following combination treatment with L-DOS47 + pemetrexed/carboplatin. For patients to be evaluable for stable disease, the duration of stable disease must be at least 42 days from the first dose of study treatment.

Exploratory Objectives:

- Evaluation of the pharmacokinetics of L-DOS47 in combination treatment with pemetrexed/carboplatin
- Evaluation of the immunogenicity of L-DOS47

Methodology:

This is a Phase I open label, dose-escalation study to evaluate the safety and tolerability of ascending doses of L-DOS47 in combination with standard doublet chemotherapy of pemetrexed/carboplatin in patients with Stage IV (TNM M1a and M1b) non-squamous non-small cell lung cancer. The study will utilize a**n accelerated "1 + 2" design up to 6µg/kg and** standard "3 + 3" design **for the final two dosing cohorts**. Patients will be recruited into cohorts of L-DOS47 escalating doses. The starting dose of L-DOS47 will be 0.59 µg/kg. The standard of care doses of pemetrexed [500 mg/m^2] and carboplatin [AUC_6], respectively, to be administered in combination with L-DOS47, will remain constant across cohorts.

All patients at a given dose level must complete Cycle 1 before escalation in subsequent patients can proceed. The decision for dose escalation to the next dose level will be made after the safety data have been reviewed by a Safety Review Committee, consisting of the Investigators, the Medical Monitor, and the Sponsor.

Dose escalation will be based on dose limiting toxicities (DLTs).

The starting dose of L-DOS47 will be 0.59 µg/kg, administered by intravenous infusion over 30 minutes. Patients will receive L-DOS47 in combination with standard chemotherapy of pemetrexed/carboplatin [pemetrexed 500 mg/m^2 over 10 min and carboplatin AUC_6 mg/mL over 30 min every 3 weeks]. The sequence of administration of the combination therapy on Day 1 of each treatment cycle is as follows: 1) pemetrexed intravenous infusion over 10 minutes; 2) approximately 30 minutes after the end of the pemetrexed infusion, carboplatin intravenously infused over 30 minutes; 3) approximately 30 minutes after the end of the carboplatin infusion, L-DOS47 will be intravenously infused over 30 minutes. L-DOS47 infusion may be increased to 60 minutes in the event of a mild infusion reaction. The infusion bag for L-DOS47 must be used within 3 hours of preparation. A treatment cycle will be 21 days, with patients receiving L-DOS47 on Days 1, 8, and 15 and pemetrexed/carboplatin on Day 1 of each treatment cycle.

It is planned that patients will receive 4 cycles of combination treatment with L-DOS47 + pemetrexed/carboplatin. Patients who have not progressed following the 4 cycles of combination treatment and who have not experienced unacceptable toxicity will have the opportunity to continue to receive additional cycles of L-DOS47 treatment for as long as there is clinical benefit and it is well-tolerated, in the opinion of the Investigator, until disease progression. Patients who are unable to complete 4 cycles of L-DOS47 + pemetrexed/carboplatin combination treatment due to pemetrexed/carboplatin toxicity will have the opportunity to continue receiving L-DOS47 treatment following discontinuation of pemetrexed/carboplatin, for as long as there is clinical benefit and it is well-tolerated, in the opinion of the Investigator, until disease progression.

Number of patients: It is anticipated that up to **37** patients will be enrolled in this study (estimation based on **3 patients per cohort for 5 dose escalations,** 6 patients per cohort for **2** dose escalation cohorts and 10 patients in the MTD expansion cohort).

Diagnosis and main criteria for inclusion:
Patients may be entered in the study only if they meet all of the following criteria:

1. Male or female patient ≥ 18 years of age;
2. Histologically or cytologically confirmed non-squamous NSCLC, classified as:
    - Chemotherapy-naive Stage IV (TNM M1a or M1b) non-squamous NSCLC for whom pemetrexed/carboplatin would be appropriate therapy
    - Stage IV (TNM M1a or M1b) non-squamous NSCLC recurrent following prior surgery, radiation and/or adjuvant chemotherapy, for whom pemetrexed/carboplatin would be appropriate therapy
    - Staging of non-squamous NSCLC must be assessed according to TNM, 7th edition and based on computed tomography (CT) scan;
3. EGFR-mutation positive patients must have progressed on or had intolerance to an EGFR small molecule tyrosine kinase inhibitor. The washout period for patients treated with an EGFR tyrosine kinase inhibitor is 7 days10;
4. Patients whose tumors harbor an anaplastic lymphoma kinase (ALK) translocation must have progressed on or had intolerance to an ALK inhibitor. The washout period for patients treated with an ALK inhibitor is 7 days11;
5. No prior adjuvant chemotherapy within 6 months of the first treatment day if there is recurrent disease;
6. At least 1 site of measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1;
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and minimum life expectancy of ≥ 3 months;
8. Adequate bone marrow function defined as: absolute neutrophil count (ANC) ≥ 1.5 x 109/L, hemoglobin ≥ 9 g/dL, and platelet count ≥100 x 109/L;
9. Adequate renal function defined as creatinine ≤1.5 x institutional upper limit of normal (ULN);
10. Adequate liver function defined as: total bilirubin ≤1.5 x institutional ULN and not increasing more than 25% within the last 4 weeks, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x institutional ULN, or < 5 x ULN if liver abnormalities are due to underlying malignancy;
11. Male or female patients of child-producing potential must agree to use an effective method of contraception during the study and for 90 days after the last day of treatment;
12. Females of childbearing potential must have a negative serum pregnancy test;
13. Females must not be breastfeeding;
14. Ability to understand study procedures and provision of signed and dated written informed consent prior to any study specific procedures;
15. Patients with treated and stable brain metastases as documented by repeat MRI showing stabilization one month after definitive response
    - Patients must be off steroids and not taking antiepileptics for brain metastases.

Main Exclusion Criteria:
Patients will not be entered in the study for any of the following reasons:

1. Histologic evidence of predominantly squamous cell NSCLC;
2. Patients with brain metastasis unless asymptomatic, not requiring steroids or antiseizure medications, and treated and stable for at least 4 weeks prior to start of study treatment;
3. Peripheral neuropathy > CTCAE grade 1;
4. Possibility of a curative local treatment (surgery and/or radiotherapy);
5. Previous chemotherapy except adjuvant treatment with progression of disease documented ≥ 6 months after end of adjuvant treatment;

6. Having received treatment in another clinical study within the 30 days prior to commencing study treatment or having side effects of a prior study drug that are not recovered to grade ≤ 1 or baseline, except for alopecia;
7. Concurrent chronic systemic immunotherapy, chemotherapy or hormone therapy;
8. Chronic treatment with systemic steroids (other than inhalers or topical steroids) or other medications to suppress the immune system; acute steroid use is permissible**;**
9. Significant cardiac disease including heart failure that meets New York Heart Association (NYHA) class III and IV definitions, history of myocardial infarction within six months of study entry, uncontrolled dysrhythmias or poorly controlled angina;
10. Sustained QTc (the QT interval corrected for heart rate) with Fridericia's correction > 470 ms at screening or a history of additional risk factors for Torsades de Pointes (e.g., heart failure, hypokalemia, family history of long QT syndrome);
11. Known positive human immunodeficiency virus (HIV), known hepatitis B surface antigen positivity, or hepatitis C antibody positivity;
12. Previous malignancy within the last 5 years (except history of basal cell carcinoma of skin or pre-invasive carcinoma of the cervix with adequate treatment);
13. Serious uncontrolled medical condition, other life-threatening illness, significant organ dysfunction, or clinically significant laboratory abnormality, which in the opinion of the Investigator, would either compromise the patient's safety or interfere with evaluation of the safety of the study treatment;
14. History of severe psychiatric illness;
15. Dementia or significantly altered mental status that would prohibit the understanding or rendering of informed consent or compliance with the requirements of the protocol;
16. Life expectancy of < 3 months;
17. Known hypersensitivity reaction to any of the components of the study treatment;
18. Pregnancy (absence to be confirmed by ß-hCG test) or breastfeeding;
19. History of hepatic encephalopathy;
20. Presence of interstitial pneumonitis.

Test product, dose and mode of administration, batch no.:

Test Product L-DOS47

L-DOS47 drug product is provided as a lyophilized cake in 3 mL stoppered and crimped Type I glass vials intended for reconstitution for i.v. infusion in normal saline (0.9% NaCl) solution with 0.02% polysorbate 80. L-DOS47 should be stored at 2-8°C.

L-DOS47 will be administered at a starting dose of 0.59 µg/kg by intravenous infusion over 30 minutes.

Doublet Chemotherapy

Carboplatin:

Carboplatin will be prepared as described in the drug package insert. It will be administered by intravenous infusion at a dose of AUC_6 mg/mL over 30 minutes.

Pemetrexed:

Pemetrexed will be prepared as described in the prescribing information sheet. It will be administered by intravenous infusion at a dose of 500 mg/m^2 over 10 minutes.

Pemetrexed Pre-medication:

Vitamin Supplementation

Instruct patients to initiate folic acid 400 µg to 1000 µg orally once daily beginning 7 days before the first dose of pemetrexed. Continue folic acid during the full course of therapy and for 21 days after the last dose of pemetrexed.

Administer vitamin B12 1 mg intramuscularly 1 week prior to the first dose of pemetrexed and every 3 cycles thereafter. Subsequent vitamin B12 injections may be given the same day as treatment with pemetrexed.

Corticosteroids

Administer dexamethasone 4 mg orally twice daily the day before, the day of, and the day after pemetrexed administration.

Dose Escalation Scheme:

The dose escalation scheme is described in the table below:

Cohort	L-DOS47 Dose in µg/kg
-1*	0.46
1	0.59
2	0.78
3	1.5
4	3.0
5	6.0
6	9.0
7	12.0

*If the starting dose level results in DLT, patients will be treated at the -1 dose level.

Dose limiting Toxicity (DLT):

In the accelerated dose escalation phase of the study, dose limiting toxicity (DLT) is defined as the occurrence of any of the following events (according to NCI CTCAE version 4.0) that are considered to be related to L-DOS47:

- **Hematologic adverse events ≥ grade 4**
- **Non-hematologic adverse events ≥ grade 3**

- **One instance each of two unique grade 2 adverse events**

that occur within 21 days after commencing study drug treatment considered to be possibly, probably, or definitely related to L-DOS47 by the Investigator.

In the standard dose escalation phase, a DLT is defined as the occurrence of any of the following events (according to NCI CTCAE version 4.0):

- Hematologic adverse events ≥ grade 4
- Non-hematologic adverse events ≥ grade 3

that occur within 21 days after commencing study drug treatment considered to be possibly, probably, or definitely related to study drug treatment by the Investigator.

For the purpose of cohort evaluation, if a patient does not receive all of his/her scheduled L-DOS47 doses in Cycle 1 due to toxicity, this will be considered a DLT.

Patients experiencing a DLT during the first treatment cycle will be withdrawn from the study.

Dose escalation and determination of maximum tolerated dose (MTD) and recommended dose (RD) for Phase II:

Dose escalation will proceed according to the following scheme based on DLTs occurring during the first cycle of treatment.

During the accelerated design phase (Cohorts 1 – 5)

No. of Patients with DLT at a Given Dose Level	**Escalation Decision Rule**
0 out of 1	**Enter patient(s) at the next dose level.**
1 out of 1	**Enter at least 2 more patients at this dose level.** • **If 0 of these 2 patients experiences DLT, proceed to the next dose level.** • **If 1 or more of this group suffer DLT, then dose escalation is stopped and this dose is declared the maximally administered dose. A total of 6 patients will be dosed at the next lowest dose level.**
1 out of 1	**Enter an additional 3 patients at this dose level, if the patient suffers a DLT as a result of one instance each of two unique grade 2 adverse events. Escalation decision will be based on standard design rules for these additional patients.**
≤ 1 out of 6 at highest dose level below the maximally administered dose	**This will be the Recommended Phase II Dose. At least 6 patients will be entered at this dose.**

During the standard design phase (Cohorts 6 and 7)

No. of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter patient(s) at the next dose level.
≥ 2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose level.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experiences DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped and this dose is declared the maximally administered dose. Three additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤ 1 out of 6 at highest dose level below the maximally administered dose	This will be the Recommended Phase II Dose. At least 6 patients will be entered at this dose.

The MTD/RD is defined as the highest dose level at which ≤ 1 of 6 patients experience a dose limiting toxicity during the first treatment cycle.

MTD Confirmation Cohort:

Once the MTD is defined, a confirmation cohort of approximately 10 patients will be enrolled at the MTD to determine the recommended Phase II dose for the combination treatment.

Criteria for retreatment:

Criteria for retreatment on Day 1:
The following criteria must be met in order for the patient to initiate therapy on Day 1 of any cycle:
ANC ≥ 1.5 x 10^9/L
Platelet count ≥ 100 x 10^9/L

Criteria for retreatment on Days 8 and 15:
Toxicity considered by the Investigator to be related to therapy with L-DOS47 (except alopecia or anemia) must have resolved to ≤ Grade 2, or to a level considered acceptable by the Investigator, or to the patient's baseline values.

Dose modifications:

Dose reductions/modifications for L-DOS47

If a patient experiences an AE meeting the definition of DLT (see Section 6.1.5), the patient will be withdrawn from the study and will not receive further doses of L-DOS47. Any AE occurring after the defined DLT criteria window will not be considered a DLT.

The table below provides a list of L-DOS47 doses and dose reductions for each cohort. Criteria for dose reductions are described in Section 6.2.

Dosing schedule for each treatment cycle (including dose reductions)

Cohort	Dose (µg/kg)	Dose Reduction (µg/kg)
1	0.59	0.46 (-1 Dose)
2	0.78	0.59
3	1.5	0.78
4	3.0	1.5
5	6.0	3.0
6	9.0	6.0
7	12.0	9.0

To meet the criteria for retreatment, all toxicities considered by the Investigator to be related to therapy with L-DOS47 (except alopecia or anemia) must have resolved to ≤ Grade 2, or to a level considered acceptable by the Investigator, or to the patient's baseline values.

If the patient does not meet the retreatment criteria, the dose will be held and the patient should be reassessed weekly (or sooner if deemed clinically appropriate) for possibility of retreatment. If treatment is delayed for more than 14 days, the patient should be withdrawn from the study, unless discussed and agreed with the Medical Monitor.

Dose delay/modifications

Dose modification for subsequent cycles is required when any of the dose delay conditions in the table below or L-DOS47 toxicity criteria are met. Only one dose level reduction is allowed as outlined in the table above.

In making the decision for dose modification, the worst case scenario should be used.

Dose delay definitions

Dose delay	Occurrence	Action for L-DOS47
Up to 7 days	1st	None
Up to 7 days	2nd	Dose Reduction
Up to 7 days	3rd	Withdrawn[1]
8 to 14 days	1st	Dose Reduction
8 to 14 days	2nd	Withdrawn[1]

[1] The withdrawal of patients from study will be discussed with the Medical Monitor. A decision to not withdraw a patient must be agreed upon by the Sponsor and Medical Monitor, clinically supported and documented.

Toxicity criteria for L-DOS47 dose modification

Toxicity	Grade	Occurrence	Relationship	Action for L-DOS47
Hematological				
Neutropenia				

	3 or 4	Any	Possible, probable, definite	None
	3 or 4	Any, prior delay of dosing	Possible, probable, definite	Dose Reduction
	3 or 4	2nd, prior dose reduction	Possible, probable, definite	Withdrawn[1]
Thrombocytopenia[2]				
	3 or 4	Any	Possible, probable, definite	None
	3 or 4	Any, prior delay of dosing	Possible, probable, definite	Dose Reduction
	3 or 4	2nd, prior dose reduction	Possible, probable, definite	Withdrawn[1]
Bleeding				
	1 or 2	1st	Possible, probable, definite	Dose Reduction
	1 or 2	Any, prior dose reduction	Possible, probable, definite	Withdrawn[1]
	3 or 4	1st	Possible, probable, definite	Withdrawn[1]
Non-Hematological				
	3	1st	Possible, probable, definite	Dose Reduction
	3	2nd, prior dose reduction	Possible, probable, definite	Withdrawn[1]
	4	1st	Possible, probable, definite	Withdrawn[1]

[1] The withdrawal of patients from study will be discussed with the Medical Monitor. A decision to not withdraw a patient must be agreed upon by the Sponsor and Medical Monitor, clinically supported and documented.
[2.] Without bleeding or platelet transfusion.

Dose reductions/modifications for pemetrexed and carboplatin:

Doses will be reduced for hematological and other adverse events. Dose adjustments are to be made according to the system showing the greatest degree of toxicity, graded using the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE).

Any patient who requires a dose reduction will continue to receive a reduced dose for the remainder of the study. Any patient with 2 prior dose reductions who experiences a toxicity that would cause a third dose reduction must discontinue from pemetrexed and carboplatin therapy.

Hematologic Toxicity

Dose adjustments at the start of a subsequent cycle of therapy will be based on platelet and neutrophil nadir (lowest value) counts from the preceding cycle of therapy. ANC must be $\geq 1.5 \times 10^9$/L and platelets $\geq 100 \times 10^9$/L prior to the start of any cycle. Treatment should be delayed to allow sufficient time for recovery. Upon recovery, if treatment is resumed, it should be according to the guidelines in the table below.

Dose adjustments for pemetrexed and carboplatin based on nadir hematologic values for preceding cycle

Abbreviation: ANC = absolute neutrophil count.

Platelets (x 10^9/L) Nadir		ANC (x 10^9/L) Nadir	Percent of Previous Dose
> 50	and	>0.5	100%
> 50	and	< 0.5	75%
< 50	and	any	75%
< 50 + bleeding	and	any	50%
any	and	< 1.0 + fever of ≥ 38.5°C	75%
Recurrence of Grade 3 or 4 thrombocytopenia after 2 dose reductions		Recurrence of Grade 3 or 4 neutropenia after 2 dose reductions	Discontinue pemetrexed and carboplatin

Non-hematologic toxicity

In the event of diarrhea requiring hospitalization (or of at least Grade 3), treatment should be delayed until diarrhea has resolved before proceeding. Treatment with pemetrexed should be resumed at 75% of the previous dose level. The carboplatin should remain the same.

For other non-hematologic effects greater than or equal to Grade 3, with the exception of alopecia and mucositis, treatment must be delayed until resolution to less than or equal to the patient's baseline CTCAE grade before proceeding. Treatment should resume at 75% of the previous dose level if deemed appropriate by the treating physician. For Grade 3 or 4 transaminase elevations, the drug dose level should not be reduced.

Dose modifications for pemetrexed and carboplatin for mucositis

	Dose for Next Cycle	
CTCAE Grade	**Pemetrexed**	**Carboplatin (AUC)**
Grade 0-2	100% of previous dose	100% of previous dose
Grade 3-4	50% of previous dose	100% of previous dose
Recurrence of Grade 3 or 4 after treatment at 2 dose reductions	Discontinue pemetrexed	Discontinue carboplatin

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events

Dose modifications for pemetrexed and carboplatin in case of neurosensory toxicity	**Dose for Next Cycle**	
CTCAE Grade	**Pemetrexed**	**Carboplatin (AUC)**
Grade 0-1	100% of previous dose	100% of previous dose
Grade 2	100% of previous dose	50% of previous dose
Grade 3-4 (or recurrence of Grade 2 after treatment at dose reduction for Carboplatin)	Discontinue pemetrexed	Discontinue carboplatin

Abbreviations: AUC = area under the curve; CTCAE = Common Terminology Criteria for Adverse Events

Duration of treatment:

It is planned that patients will receive up to 4 cycles of combination treatment with L-DOS47 + pemetrexed/carboplatin. Patients who have not progressed following the 4 cycles of combination treatment and who have not experienced unacceptable toxicity will have the opportunity to continue to receive additional cycles of L-DOS47 treatment for as long as there is clinical benefit and it is well-

tolerated, in the opinion of the Investigator, until disease progression. Patients who are unable to complete 4 cycles of L-DOS47 + pemetrexed/carboplatin combination treatment due to pemetrexed/carboplatin toxicity will have the opportunity to continue to receive additional cycles of L-DOS47 treatment following discontinuation of pemetrexed/carboplatin, for as long as there is clinical benefit and it is well-tolerated, in the opinion of the Investigator, until disease progression.

Reference therapy, dose and mode of administration, batch no.:

Not applicable.

Criteria for evaluation:

Safety:

Safety data will be reported for all patients who received any amount of L-DOS47. These data will include vital signs, laboratory parameters, and adverse events. The severity of adverse events and laboratory abnormalities will be reported according to NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

DLTs, SAEs, AEs leading to treatment discontinuation, and the MTD of L-DOS47 in combination with pemetrexed/carboplatin doublet chemotherapy will be determined. Once the MTD is defined, a confirmation cohort of approximately 10 patients will be enrolled at the MTD to determine the recommended Phase II doses for the combination treatment.

Efficacy:

Objective response assessment will be performed at baseline, after every 2 cycles, and at off-study using the same method of radiologic imaging at each assessment. Objective tumor response will be assessed according to RECIST version 1.1 in patients who have completed at least 2 cycles of study treatment and who have at least 1 post-treatment disease assessment. For patients with fewer than 2 cycles of study treatment, there must be clear evidence of clinical progression to be considered evaluable for efficacy.

Exploratory:

Pharmacokinetic parameters for L-DOS47 will be determined from plasma samples collected from all patients at the following timepoints:

Cycle 1, Days 1 and 8: predose and serially postdose (time relative to the start of infusion) at 15 (during infusion), 30 (prior to end of infusion)*, 45 minutes* and 1*, 1.5, 2, 3, 4, 24, and 48 hours postdose; Cycles 2 and 4, Day 8: predose and serially postdose (time relative to the start of infusion) at 15 (during infusion), 30 (prior to end of infusion)*, 45 minutes* and 1*, 1.5, 2, 3, 4, and 24 hours postdose; Cycle 2, Day 1; Cycle 3, Days 1 and 8; Cycle 4, Day 1: predose and 30 minutes* postdose (time relative to the start of infusion, to be collected just prior to end of infusion).

* If the L-DOS47 infusion time is increased from 30 minutes to 60 minutes in the event of a mild infusion reaction, there will be no change in the PK sampling timepoints, which are all relative to the start of L-DOS47 infusion. PK samples collected at 30 minutes and 45 minutes will be considered during infusion samples and PK sample collected at 60 minutes (1 hour) will be a prior to end of infusion sample. All other timepoints remain the same.

Tumor antigen (CEACAM6) assessment: blood samples will be drawn (predose [0 hours]) on Day 1 (predose [0 hours]) of Cycle 2 and on Day 8 of Cycle 4 or the End of Treatment Visit (whichever

occurs first).

The immunogenicity of L-DOS47 will be evaluated from serum samples collected on Cycle 1, Day 1 (predose; baseline) and Day 8 (predose), Cycles 2 through 4 (Day 1, predose), all additional cycles (i.e., Cycle 5 and beyond, Day 1 (predose), at the end of treatment or early termination visit, and at the follow-up visit (30 days after the last dose).

Statistical methods:
Demographic data will be displayed and descriptive summary statistics will be used to describe the study population (e.g., ranges, mean and medians of age, and weight; numbers of males and females; description of baseline performance status characteristics; tabulation of tumor types and histology).

Safety data will be tabulated for all patients who receive any amount of study treatment. These data will include laboratory parameters, adverse events, and cardiographic values. The tabulation of laboratory parameters will indicate the normal ranges for each parameter. Each value will be classified as falling above, below, or within the normal range.

Adverse events will be tabulated by body system, severity and relation to treatment. For the purposes of presentation, groups will be arranged by decreasing frequency of adverse events.

Efficacy data will be tabulated. The best overall response rate, defined using RECIST 1.1, will be summarized for efficacy-evaluable patients. The percentage of patients in each of the best overall response categories will be presented. The overall response rate will be calculated as the proportion of patients with responsive disease (CR and PR). Clinical benefit will be calculated as the percentage of patients achieving complete response, partial response, and stable disease. For patients to be evaluable for stable disease, the duration of stable disease must be at least 42 days from the first dose of study treatment. Clinical benefit data from all cohorts will be displayed in a waterfall plot.

Pharmacokinetic parameters will be determined from L-DOS47 concentrations using non-compartmental methods (WinNonLin®). L-DOS47 PK parameters to be calculated (if adequate data are available for estimation) will include maximum concentration (C_{max}), time of C_{max} (T_{max}), applicable area under the curve (AUC) parameters, terminal half-life ($t_{½}$), systemic clearance (CL), volumes of distribution (V_z) and volume of distribution at steady state (V_{ss}) and urinary excretion parameters. The concentrations and PK parameters will be summarized using descriptive statistics (n, mean, standard deviation, percent coefficient of variation, geometric mean, median, minimum and maximum).

Immunogenicity data will be tabulated. The concentration of anti-L-DOS47 antibodies will be evaluated using descriptive statistics.

LIST OF ABBREVIATIONS

AE	Adverse event
AFAIKL2	Recombinant camelid single domain antibody
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BP	Blood pressure
CEACAM6	Carcinoembryonic antigen-related cell adhesion molecule 6
CL	Systemic clearance
C_{max}	Maximum observed plasma concentration after dosing
CNS	Central nervous system
CR	Complete response
CrCl	Creatinine Clearance
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GLP	Good Laboratory Practice
GM-CSF	Granulocyte macrophage colony-stimulating factor
hCG	Human chorionic gonadotropin
HGB	Hemoglobin
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator's Brochure
i.v.	Intravenous
ICH	International Conference on Harmonization
IFN	Interferon (e.g, IFN-γ)
Ig	Immunoglobulin (e.g., IgG)

IL	Interleukin (e.g., IL-2)
IP	Interferon gamma-induced protein (e.g., IP-10)
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intent-to-Treat
MABEL	Minimum Anticipated Biological Effect Level
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NOAEL	No observed adverse effect level
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
PD	Progressive disease
PD	Pharmacodynamic
PK	Pharmacokinetic
PFS	Progression-Free Survival
PR	Partial response
PT	Prothrombin time
QT	A measure of the time between the start of the Q wave and the end of the T wave
QTc	The QT interval corrected for heart rate
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumour
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
t½	Terminal elimination half-life
TK	Toxicokinetic
T_{max}	Time of maximum observed plasma drug concentration after dosing
TNF	Tumor necrosis factor (e.g., TNF-α)
TNM	Tumor, Node, Metastasis tumor staging classification
TTP	Time to disease progression

ULN	Upper limit of normal
V_{ss}	Volume of distribution at steady state
V_z	Volume of distribution
WBC	White blood cell

1.0 GENERAL INFORMATION

1.1 Protocol Number and Title of the Study

A Phase I, Open Label, Dose Escalation Study of Immunoconjugate L-DOS47 in Combination with Standard Doublet Therapy of Pemetrexed/Carboplatin in Patients with Stage IV (TNM M1a or M1b) Recurrent or Metastatic Non-Squamous Non-Small Cell Lung Cancer.
Helix Protocol No. LDOS001; Theradex Protocol No. H13-11042.

1.2 Sponsor

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1.4 Signature Authorization

Theradex® will act as the Sponsor Representative.

1.5 Investigators and Institutions

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2.0 BACKGROUND INFORMATION

2.1 Introduction

Advanced lung cancer is a serious and life-threatening illness with a poor prognosis. Due to the difficulty in destroying solid tumors a fairly toxic treatment is generally required to kill the cancer cells. Research has explored the tumor microenvironment in order to exploit it in developing anticancer therapy. It has been observed that human solid tumors produce an acidic local microenvironment. This phenomenon can impact the efficacy of certain chemotherapeutics by altering their partitioning coefficient between extracellular and intracellular compartments due to charge alternations.[1, 2, 3, 4, 5] This metabolic condition can also induce metastasis and confer a growth advantage to certain cancers.

Helix BioPharma Corp. has developed an immunoconjugate cancer therapeutic to exploit the acidic tumor 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 tumor marker. The urease and the AFAIKL2 antibody are chemically conjugated by a hetero-bifunctional cross linker yielding a final product with an antibody-to-enzyme ratio of 8-10:1. CEACAM6 is a glycosylphosphatidylinositol (GPI)-anchored cell adhesion molecule that is overexpressed in many cancers that 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.[6]

When targeted to lung tumors by the AFAIKL2 mAb at an appropriate i.v. dose, L-DOS47 can potentially kill the tumor cells through alkalinization of the local milieu and production of ammonia.

However, as with many cancer treatments, at higher doses L-DOS47 has the potential to induce undesirable toxic effects. The primary goals of this Phase I study are to determine the safety and tolerability, and to establish maximum tolerated dose (MTD) and recommended Phase II dose of L-DOS47 in combination with standard doublet chemotherapy of pemetrexed/carboplatin in patients with Stage IV (TNM M1a and M1b) recurrent or metastatic non-squamous non-small cell lung cancer (NSCLC).

2.2 The Investigational Product

L-DOS47 drug substance is an immunoconjugate of approximately 680 kDa comprising a single urease hexamer covalently linked to multiple molecules of AFAIKL2, a recombinant camelid single domain antibody directed against CEACAM6. AFAIKL2 is a recombinant protein expressed in *E. coli*; urease is sourced from jack beans.

The AFAIKL2 portion of L-DOS47 active substance functions as a targeting molecule, delivering the enzyme to the tumor, where it acts to raise the pH of the cellular microenvironment through conversion of urea to ammonia and carbon dioxide. The resulting high local concentration of ammonia leads to cell death. The increased pH may also facilitate tumor cell cytotoxicity by co-administered chemotherapeutic agents.

L-DOS47 drug product is provided to the clinic in 3 mL stoppered and crimped Type I glass vials, intended for reconstitution for i.v. infusion with normal saline (0.9% NaCl) solution with 0.02% polysorbate 80. The product is a white to practically white solid before reconstitution. After reconstitution, the product is a clear and colorless to slightly yellow liquid which may contain some translucent particles. The composition (before reconstitution) of L-DOS47 is as follows:

Table 1. Composition of L-DOS47

Ingredient	Amount/Concentration	Function	Quality Standard
L-DOS47	1.7 mg/mL	Active ingredient	Internal standard
L-histidine	10 mM	Buffering agent	USP
Disodium EDTA	02 mM	Chelating agent	USP
Sucrose	1%	Stabilizer	NF

Stability studies indicate that the drug product remains within specification for 12 months when stored between 2-8°C. Stability studies are ongoing and therefore the shelf-life may be adjusted as warranted.

L-DOS47 should be stored at 2-8°C. Detailed instructions for reconstitution of L-DOS47 are provided in the Pharmacy Manual.

2.3 Preclinical Studies

In vitro, *ex vivo*, and *in vivo* studies have been conducted to provide proof of concept data to support ongoing development of L-DOS47 and establish a safety/tolerability profile to support clinical development. The specificity of L-DOS47 for lung cancer cells expressing CEACAM6 on the cell surface was assessed through *in vitro* binding studies, demonstrating that L-DOS47

binds with high affinity to the human CEACAM6 antigen. This result was confirmed in an *ex vivo* binding assessment of L-DOS47 to human malignant tumor sections, where the antibody component of L-DOS47 bound robustly and significantly to human lung carcinoma tissue sections. Inhibition of CEACAM6 expression by gene knockdown technology prevented L-DOS47 binding, further highlighting the specificity of the immunoconjugate targeting moiety for CEACAM6. The specific, targeted function of the L-DOS47 antibody for human tumors has been confirmed *in vivo* in biodistribution studies conducted in nude mice human tumor xenografts; L-DOS47 is observed at the tumor site 12 hours post injection and accumulation continues for up to 48 hours post-dosing. Additional *in vitro* studies indicated that an enzyme to antibody conjugation ratio of greater than 8:1 was optimal for L-DOS47 binding to CEACAM6.

The mechanism of action of L-DOS47 was investigated through *in vitro* and *in vivo* pharmacodynamic (PD) studies. Urease is the active component of L-DOS47, and studies demonstrated that urease is cytotoxic to human tumor cells *in vitro*, and intratumoral administration of urease to A549 (lung adenocarcinoma) and MCF 7 (breast cancer) tumors in nude mice xenograft models inhibits tumor growth. L-DOS47 was observed to bind with high affinity to two human tumor cell lines, BxPC-3 (pancreatic) and A549 (lung), with binding affinity/avidity shown as BxPC-3>A549. The cytotoxic effect of L-DOS47 in these cell lines corresponded to the binding affinity. *In vivo* studies confirmed this cytotoxic effect, with intravenous (i.v.) administration of L-DOS47 to nude mouse tumor xenograft models of pancreatic adenocarcinoma (BxPC-3) and lung adenocarcinoma (A549) inhibiting tumor growth.

Six toxicology studies have been conducted to establish the safety and tolerability of L-DOS47. Single-dose i.v. toxicity has established the maximum tolerated dose (MTD) of L-DOS47 as 520 μg/kg in Sprague-Dawley rats and 70 μg/kg in cynomolgus monkeys.

Pharmacology was assessed by repeat-dosing of L-DOS47 in Sprague-Dawley rats and cynomolgus monkeys. In rats, pre-terminal deaths were recorded when dosing with 170-255 μg/kg L-DOS47, where clinical observations associated with toxicity included decreased activity, laboured breathing, production of vomitus or uncharacteristic liquid material, and tremors or sustained convulsions. Histopathologic analysis identified some liver pathology when L-DOS47 is administered at dose levels ≥ 210 μg/kg. The no observed adverse effect level (NOAEL) in rats is considered to be 85 μg/kg/dose.

Repeat i.v. dosing of L-DOS47 in cynomolgus monkeys established the NOAEL to be 26 μg/kg L-DOS47, where one death was recorded following the first dosing of 35 μg/kg. The 4-week repeated administration of 60 μg/kg was tolerated in a non-Good Laboratory Practice (GLP) compliant study; however, this dose was associated with clinical signs of toxicity that were consistent with those observed in the rat model. Clinical signs of toxicity are consistently observed within 1-2 hours of dose administration.

In the repeat-dose toxicity study in monkeys, cardiovascular parameters were assessed through electrocardiograms (ECGs), monitoring of blood pressure and heart rate, both pre-treatment and at Week 4. Respiratory rate was also examined in all animals once prior to commencement of treatment and at Week 4. The results of these tests demonstrated that there was no L-DOS47-related effect on heart rate, blood pressure, respiratory rate, and ECG measurements in the monkeys over the course of the study.

Administration of L-DOS47 did not elicit dose-dependent changes in cytokine release *in vitro* in all species assayed. Similarly, changes in the production of cytokines in rats following 4-weekly injections of L-DOS47 were not attributable to dosing with the test article. Changes in the concentrations of Interleukin-2 (IL-2) and granulocyte macrophage colony-stimulating factor (GM-CSF) in monkeys following repeat dosing of L-DOS47 were inconsistent with those observed in control groups however, and therefore these effects may be treatment-related. No change in the concentrations of other cytokines was observed in monkeys following L-DOS47 dosing, and no consistent dose-dependent changes in cytokine release were apparent.

The administration of L-DOS47 elicited production of anti-LDOS47 immunoglobulin G (IgG) and IgM antibodies in rats at all dose levels, and appeared to be dose-dependent in males. The magnitude of the immunogenic response was greater in females, where the antibody titre was consistently higher across all treatment groups. The generation of anti-drug antibodies by Day 15 following repeat dose administration of L-DOS47 was consistent with toxicokinetic (TK) data, which highlighted a high degree of inter-animal variability in plasma L-DOS47 concentrations following dosing on Day 22. The half-life of L-DOS47 ranged from 6.35 to 13.5 hours in rats. Toxicokinetic analysis demonstrated no accumulation of L-DOS47 over 4-weekly injections, and an approximately proportional dose-dependent increase in exposure on Day 1 was noted.

Immunogenicity analysis of serum samples 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 as determined by TK analysis. The half-life of L-DOS47 generally ranged from 7 to 13 hours in monkeys. Similar to that observed following repeat dosing of rats, no L-DOS47 accumulation was apparent over the duration of dosing.

Whilst the reproductive toxicity of L-DOS47 has not been directly assessed, histopathology of reproductive organs identified no signs of toxicity following repeat dosing of both rats and monkeys. Assessment of the local tolerance following administration of the test article similarly indicated that L-DOS47 is well tolerated across all dose levels in both rats and monkeys.

The nonclinical development of L-DOS47 has established the efficacy and safety profile of L-DOS47. Clinical development of L-DOS47 is being undertaken, with the view of providing critical data such as an evaluation of immunogenicity of L-DOS47 in tumor-bearing patients

over potentially multiple cycles of therapy, the stability of the L-DOS47 immunoconjugate prior to targeting, as well as the pharmacokinetics (PK) of L-DOS47.

2.4 Previous Clinical Studies

A first-in-human clinical trial with L-DOS47 has been initiated in Poland **(LDOS002)**. It is a Phase I/II, open label, non-randomized, dose escalation study of L-DOS47 monotherapy in patients with non-squamous non-small cell lung cancer (NSCLC).

The primary objective of the Phase I portion of the trial is to define the MTD of multiple doses of L-DOS47 administered i.v. to patients with non-squamous NSCLC. The primary objective of the Phase II portion is to make a preliminary assessment of the efficacy of L-DOS47 in patients with non-squamous NSCLC.

The secondary objectives of both phases of the study are to evaluate the pharmacokinetics of L-DOS47, the immunogenicity, and the safety and tolerability of L-DOS47 in these patients.

A total of 55 patients received doses of L-DOS47 ranging from 0.12 µg/kg to 13.55 µg/kg in the phase I component of study LDOS002. The most common adverse events (AEs) were dyspnoea, fatigue, anaemia, nausea, insomnia and decreased appetite. During the treatment period, serial blood samples (serum) were collected for the measurement of cytokines. Brief increases in cytokines IL-6, IL-8, IL-12, IP-10 and TNFα were observed. These were not observed in all patients or all dose levels studied. There were no trends observed in the data that would suggest a significant shift in cytokines analyzed in Phase I patients. To date, there is no evidence that L-DOS47 elicits a dose-dependent release of cytokines in treated patients.

An assessment of L-DOS47 maximum observed plasma concentration after dosing (C_{max}) associated with morbidity and mortality in the nonclinical pivotal repeat-dose toxicology studies determined that plasma C_{max} concentrations of ≤ 899 ng/mL L-DOS47 did not result in any pre-terminal animal death. In determining a safe clinical dose for this study, the Sponsor selected a plasma C_{max} level of ≤ 500 ng/mL, approximately 1.6-fold below the dose considered safe in the repeat dose toxicology studies. The largest individual C_{max} reported following a review of pharmacokinetic (PK) data was 261.68 ng/mL, observed 50 minutes following the start of administration of the 13.55µg/kg dose at Cycle 1 Day 1.

Time of maximum observed plasma concentration after dosing (Tmax) was consistent across dose levels and treatment cycles and occurred within the first hour following the start L-DOS47 infusion. A decrease in the area under the concentration-time curve from dosing to time of last measureable concentration (AUC_{0-t}) was observed in most patients

following the Cycle 2 Day 8 dosing for all dose levels where PK data are available. This is consistent with production of anti-L-DOS47 antibodies.

The mean terminal elimination half-life (t½) of L-DOS47 for data analysed to-date administered to date range from 2.38 to 10.9 hours. This is consistent with what was observed in the nonclinical pivotal repeat-dose TK studies. There is no trend between the plasma half-life and the increase in the dose of L-DOS47. These data support a more frequent dosing of L-DOS47 than the weekly dosing schedule followed in the LDOS002 protocol.

The majority of patients in study LDOS002 developed anti-L-DOS47 antibodies during the protocol-defined treatment period. Anti-L-DOS47 antibodies are detectable as early as 8 days after the start of L-DOS47 administration. After reviewing both the PK parameters calculated for the first 12 dosing cohorts for study LDOS002 and anti-L-DOS47 antibodies measured for these patients, it is highly probable that the production of these antibodies are having an impact on L-DOS47 PK.

In this study, a total of 9 patients received doses of L-DOS47 ranging from 0.59µg/kg to 0.78µg/kg. The most common AEs reported were constipation, rash, dyspnea, decreased neutrophil and white blood cell counts. AEs reported to-date were low grade and patients recovered without sequelae. No DLTs were reported.

2.5 Potential Risks and Benefits

The Investigator Brochure may be updated during the course of this study with additional risks and benefits. Please see the current Investigator Brochure for further details about the potential risks and benefits associated with this study.

Toxic effects of L-DOS47 as seen in toxicology studies in Sprague-Dawley rats and cynomolgus monkeys appear to relate mainly to effects on the lung and CNS. Some of these toxic effects are most likely associated with increased blood levels of ammonia. Increased blood levels of ammonia have been associated with toxicity in the lung, including bronchiolar and alveolar edema and airway destruction resulting in respiratory distress or failure.[7,8,9] Increased blood levels of ammonia have also been associated with convulsions.[9] At high doses of L-DOS47 the CNS effects are likely to be the result of increased blood ammonia concentration. The facts that the results of the pivotal GLP repeat-dose toxicology studies with L-DOS47 in rat and monkey resemble those for the toxicology study with DOS47 (urease) in mice suggest that the toxicities associated with administration of high doses of L-DOS47 are due to the urease component of the conjugate.

It is anticipated that the major potential risks for this trial will be related to allergic infusion reactions and to systemic effects on untested organ systems and cells, given that the drug is administered intravenously.

Human exposure to L-DOS47 is limited to data generated from the Polish Phase I/II study (LDOS002) and the ongoing U.S. Phase I study (LDOS001). A total of 85 patients received doses of L-DOS47 ranging from 0.12µg/kg to 13.55µg/kg. Repeat administrations of L-DOS47 for doses up to 13.55µg/kg were safe and well tolerated. Only 1 AE (spinal pain) met the definition of a dose-limiting toxicity (DLT) at the dose of 5.76µg/kg in study LDOS002. Most of the events were mild to moderate in intensity and transient in duration; they subsided spontaneously during continued administration of L-DOS47. Many of the events reported were expected for the population under study. The most common adverse events (AEs) were dyspnoea, fatigue, anaemia, nausea, insomnia and decreased appetite.

In order to maximize the number of patients receiving a potentially active dose of L-DOS47, an accelerated dose design up to 6µg/kg will be implemented in this study followed by a standard 3+3 design for the final two dosing cohorts, 9 and 12 µg/kg respectively. Adverse events reported from all completed and ongoing studies support an accelerated dose design of L-DOS47 in combination with standard of care pemetrexed/carboplatin up to 6 µg/kg.

Dose escalation will be conducted with the specified increments as follows: initially, patients will receive increasing doses of L-DOS47 from 0.46 to 0.78 µg/kg (cohorts 1 to 2) using a modified Fibonacci schema. Subsequent increments then followed a modified schedule of 100% (cohorts 3, 4 and 5), 50% (cohort 6), and 33% increments (cohort 7). Cohort transition will be monitored by a Safety Review Committee consisting of the Investigators, the medical Monitor, and the Sponsor.

2.6 Characteristics of a Well-Conducted Trial

The following characteristics of an adequate and well-conducted trial will be implemented:

1. The Investigators will be well qualified by scientific training and experience.

2. Detailed electronic Case Report Forms (eCRFs) will be completed for every patient.

3. Requirements for institutional ethics review as set forth by the appropriate Institutional Review Board/Independent Ethics Committee (IRB/IEC), Title 21 Code of Federal Regulations (CFR) Part 56, the European Union Directive 2001/20/EC and its associated Detailed Guidances, European Union GCP Directive 2005/28/EC, the ICH Guideline for

Good Clinical Practice, Sections 3 and 4, and the terms of the Declaration of Helsinki (2013), will be followed.

4. Requirements for informed consent in accordance with institutional guidelines, FDA requirements as specified in Title 21 CFR, Part 50, the European Union Directive 2001/20/EC and its associated Detailed Guidances, European Union GCP Directive 2005/28/EC, the ICH Guideline for Good Clinical Practice, Section 4.8, and the terms of the Declaration of Helsinki (2013), will be followed.

5. Safety data will be recorded and evaluated.

6. Routine monitoring visits will be conducted by the Sponsor's representative (Theradex®) to ensure data accuracy.

7. Drug accountability will be strictly maintained.

8. This trial will be conducted according to Good Clinical Practice (GCP), the protocol and applicable regulatory requirements.

2.7 Patient Population

Patients with Stage IV (TNM M1a and M1b) recurrent or metastatic non-squamous non-small cell lung cancer. It is anticipated that up to **37** patients will be enrolled in this study (estimation based on **3 patients per cohort for 5 dose escalations,** 6 patients per cohort for **2** dose escalation cohorts and 10 patients in the MTD expansion cohort).

3.0 TRIAL OBJECTIVES AND PURPOSE

Primary Objectives:

- Safety and tolerability of L-DOS47 in combination treatment with pemetrexed/carboplatin
- Determination of dose limiting toxicity of L-DOS47 in combination treatment with pemetrexed/carboplatin
- Determination of maximum tolerated dose (MTD) and recommended Phase II dose of L-DOS47 in combination treatment with pemetrexed/carboplatin

Secondary Objectives:

- Objective response rate of the combination treatment according to RECIST 1.1
- Evaluation of clinical benefit, defined as the percentage of patients who have achieved complete response, partial response, and stable disease following combination treatment with L-DOS47 + pemetrexed/carboplatin. For patients to be evaluable for stable disease,

the duration of stable disease must be at least 42 days from the first dose of study treatment.

Exploratory Objectives:

- Evaluation of the pharmacokinetics of L-DOS47 in combination treatment with pemetrexed/carboplatin
- Evaluation of the immunogenicity of L-DOS47

4.0 TRIAL DESIGN

This is a Phase I open label, dose-escalation study to evaluate the safety and tolerability of ascending doses of L-DOS47 in combination with standard doublet chemotherapy of pemetrexed/carboplatin in patients with Stage IV (TNM M1a and M1b) non-squamous non-small cell lung cancer. The study will utilize a**n accelerated "1 + 2" design up to 6µg/kg and** standard "3 + 3" design **for the final two dosing cohorts**. Patients will be recruited into cohorts of L-DOS47 starting **at a** dose **of** 0.59 µg/kg. The standard of care doses of pemetrexed [500 mg/m^2] and carboplatin, [AUC_6] respectively, to be administered in combination with L-DOS47, will remain constant across cohorts.

All patients at a given dose level must complete Cycle 1 before escalation in subsequent patients can proceed. Simultaneous dosing of patients within a dosing cohort is prohibited. Patient dosing will be separated by at least 24 hours. This will allow for the assessment of possible infusion reactions and/or allergic reactions and enable communication between study centers. The decision for dose escalation to the next dose level will be made after the safety data have been reviewed by a Safety Review Committee consisting of the Investigators, the Medical Monitor, and the Sponsor.

Dose escalation will be based on dose limiting toxicities (DLTs).

The starting dose of L-DOS47 will be 0.59 µg/kg, administered by intravenous infusion over 30 minutes. Patients will receive L-DOS47 in combination with standard doublet chemotherapy of pemetrexed/carboplatin [pemetrexed 500 mg/m^2 over 10 minutes and carboplatin AUC_6 mg/mL over 30 min every 3 weeks]. The sequence of administration of the combination therapy on Day 1 of each treatment cycle is as follows: 1) pemetrexed intravenous infusion over 10 minutes; 2) approximately 30 minutes after the end of the pemetrexed infusion, carboplatin intravenously infused over 30 minutes; 3) approximately 30 minutes after the end of the carboplatin infusion, L-DOS47 will be intravenously infused over 30 minutes. L-DOS47 infusion may be increased to 60 minutes in the event of a mild infusion reaction. The infusion bag for L-DOS47 must be used within 3 hours of preparation. A treatment cycle will be 21 days, with patients receiving L-DOS47 on Days 1, 8, and 15 and pemetrexed/carboplatin on Day 1 of each treatment cycle.

4.1 Overview of Trial Design

It is planned that patients will receive 4 cycles of combination treatment with L-DOS47 + pemetrexed/carboplatin. Patients who have not progressed following the 4 cycles of combination treatment and who have not experienced unacceptable toxicity will have the opportunity to continue to receive L-DOS47 treatment for as long as there is clinical benefit and it is well-tolerated, in the opinion of the Investigator, until disease progression. Patients who are unable to complete 4 cycles of L-DOS47 + pemetrexed/carboplatin combination treatment due to pemetrexed/carboplatin toxicity will have the opportunity to continue receiving L-DOS47 treatment following discontinuation of pemetrexed/carboplatin, for as long as there is clinical benefit and it is well-tolerated, in the opinion of the Investigator, until disease progression.

4.2 End of Study

The end of the study is defined as the date of the last visit of the last patient undergoing the trial.

4.3 Minimizing Bias

This is an open-label study, and randomization will not be used.

4.4 Drug Product

L-DOS47 drug product is provided as a lyophilized cake in 3 mL stoppered and crimped Type I glass vials intended for reconstitution for i.v. infusion in normal saline (0.9% NaCl) solution with 0.02% polysorbate 80. L-DOS47 should be stored at 2-8°C.

Detailed instructions for reconstitution of L-DOS47 are provided in the Pharmacy Manual.

L-DOS47 will be administered at a starting dose of 0.59 μg/kg by intravenous infusion over 30 minutes.

4.5 Duration of Therapy

It is planned that patients will receive up to 4 cycles of combination treatment with L-DOS47 + pemetrexed/carboplatin. Patients who have not progressed following the 4 cycles of combination treatment and who have not experienced unacceptable toxicity will have the opportunity to continue to receive additional cycles of L-DOS47 treatment for as long as there is clinical benefit and it is well-tolerated, in the opinion of the Investigator, until disease progression. Patients who are unable to complete 4 cycles of L-DOS47 + pemetrexed/carboplatin combination treatment due to pemetrexed/carboplatin toxicity will have the opportunity to continue receiving L-DOS47 treatment following discontinuation of pemetrexed/carboplatin, for as long as there is clinical benefit and it is well-tolerated, in the opinion of the Investigator, until disease progression.

4.6 Trial Discontinuation

For reasonable cause, either the Investigator or the Sponsor may terminate this study prematurely. Written notification of the termination is required. Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study
- Failure of the Investigator to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements (non-compliance)
- Lack of evaluable and/or complete data
- Decision to modify the developmental plan of the drug
- A decision on the part of the Sponsor to suspend or discontinue development of the drug

4.7 Drug Accountability/Disposition of Clinical Trial Supplies

Drug accountability records will be maintained for all clinical trial supplies.

The Investigator is responsible for maintaining accurate study treatment accountability records throughout the study. The Investigator will confirm the date of receipt and contents of each consignment of study drug received.

Each use of study treatment will be documented on the eCRF.

All unused, used or partially used study treatment supplies must be returned or destroyed as per written directives from the Sponsor or designee (i.e., may be returned to a third party for destruction or may be destroyed on site, provided that the Investigator retains sufficient records of study treatments that were destroyed).

4.8 Maintenance of Randomization Codes & Emergency Code Break Procedures

Not applicable, as this is an open label study.

4.9 Registration

Prior to registration and any study-specific evaluations being performed, all patients must have given written informed consent for the study and must have completed the pre-study evaluations (see Section 7.2). Patients must meet all of the eligibility requirements listed in Section 5.0.

Patients will be registered on the study by contacting Theradex® (see the Study Operations Manual for specific instructions).

5.0 SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Inclusion Criteria

Patients may be entered in the study only if they meet all of the following criteria:

1. Male or female patient ≥ 18 years of age;
2. Histologically or cytologically confirmed non-squamous NSCLC, classified as:
    - Chemotherapy-naive Stage IV (TNM M1a or M1b) non-squamous NSCLC for whom pemetrexed/carboplatin would be appropriate therapy
    - Stage IV (TNM M1a or M1b) non-squamous NSCLC recurrent following prior surgery, radiation and/or adjuvant chemotherapy, for whom pemetrexed/carboplatin would be appropriate therapy
    - Staging of non-squamous NSCLC must be assessed according to TNM, 7th edition and based on computed tomography (CT) scan;
3. EGFR-mutation positive patients must have progressed on or had intolerance to an EGFR small molecule tyrosine kinase inhibitor. The washout period for patients treated with an EGFR tyrosine kinase inhibitor is 7 days[10];
4. Patients whose tumors harbor an anaplastic lymphoma kinase (ALK) translocation must have progressed on or had intolerance to an ALK inhibitor. The washout period for patients treated with an ALK inhibitor is 7 days[11];
5. No prior adjuvant chemotherapy within 6 months of the first treatment day if there is recurrent disease;
6. At least 1 site of measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1;
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and minimum life expectancy of ≥ 3 months;
8. Adequate bone marrow function defined as: absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L, hemoglobin ≥ 9 g/dL, and platelet count ≥100 x 10^9/L;
9. Adequate renal function defined as creatinine ≤1.5 x institutional upper limit of normal (ULN);
10. Adequate liver function defined as: total bilirubin ≤1.5 x institutional ULN and not increasing more than 25% within the last 4 weeks, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x institutional ULN, or < 5 x ULN if liver abnormalities are due to underlying malignancy;
11. Male or female patients of child-producing potential must agree to use an effective method of contraception during the study and for 90 days after the last day of treatment;
12. Females of childbearing potential must have a negative serum pregnancy test;

13. Females must not be breastfeeding;
14. Ability to understand study procedures and provision of signed and dated written informed consent prior to any study specific procedures**;**
15. Patients with treated and stable brain metastases as documented by repeat MRI showing stabilization one month after definitive response.
    - Patients must be off steroids and not taking antiepileptics for brain metastases.

5.2 Exclusion Criteria

Patients will not be entered in the study for any of the following reasons:

1. Histologic evidence of predominantly squamous cell NSCLC;
2. Patients with brain metastasis unless asymptomatic, not requiring steroids or antiseizure medications, and treated and stable for at least 4 weeks prior to start of study treatment;
3. Peripheral neuropathy > CTCAE grade 1;
4. Possibility of a curative local treatment (surgery and/or radiotherapy);
5. Previous chemotherapy except adjuvant treatment with progression of disease documented ≥ 6 months after end of adjuvant treatment;
6. Having received treatment in another clinical study within the 30 days prior to commencing study treatment or having side effects of a prior study drug that are not recovered to grade ≤ 1 or baseline, except for alopecia;
7. Concurrent chronic systemic immunotherapy, chemotherapy or hormone therapy;
8. Chronic treatment with systemic steroids (other than inhalers or topical steroids) or other medications to suppress the immune system; acute steroid use is permissible**;**
9. Significant cardiac disease including heart failure that meets New York Heart Association (NYHA) class III and IV definitions, history of myocardial infarction within six months of study entry, uncontrolled dysrhythmias or poorly controlled angina;
10. Sustained QTc (the QT interval corrected for heart rate) with Fridericia's correction > 470 ms at screening or a history of additional risk factors for Torsades de Pointes (e.g., heart failure, hypokalemia, family history of long QT syndrome);
11. Known positive human immunodeficiency virus (HIV), known hepatitis B surface antigen positivity, or hepatitis C antibody positivity;
12. Previous malignancy within the last 5 years (except history of basal cell carcinoma of skin or pre-invasive carcinoma of the cervix with adequate treatment);
13. Serious uncontrolled medical condition, other life-threatening illness, significant organ dysfunction, or clinically significant laboratory abnormality, which in the opinion of the Investigator, would either compromise the patient's safety or interfere with evaluation of the safety of the study treatment;
14. History of severe psychiatric illness;

15. Dementia or significantly altered mental status that would prohibit the understanding or rendering of informed consent or compliance with the requirements of the protocol;
16. Life expectancy of < 3 months;
17. Known hypersensitivity reaction to any of the components of the study treatment;
18. Pregnancy (absence to be confirmed by ß-hCG test) or breastfeeding;
19. History of hepatic encephalopathy;
20. Presence of interstitial pneumonitis.

5.3 Inclusion of Women, Minorities and Children

Both men and women and members of all races and ethnic groups are eligible for this study. Children are not eligible for this study because the safety and tolerability of the proposed dosing schedule has not been determined in adults.

5.4 Withdrawal Criteria

Protocol therapy will be discontinued at any time if any of the following situations occur:

1. Progressive disease.
2. The development of toxicity which, in the Investigator's judgment, precludes further therapy.
3. Patient refusal.
4. Lost to follow-up/noncompliance.
5. Intercurrent illness.
6. At the discretion of the Investigator.
7. Pregnancy.
8. Study termination.

5.4.1 Withdrawn Subjects

When a patient is removed from the study, the Investigator will clearly document the reason in the medical record and complete the appropriate case report form page describing the reason for discontinuation. In addition, every effort should be made to complete the appropriate assessments listed in Section 7.4.

5.5 Noncompliance

All instances of noncompliance and all resulting protocol deviations will be recorded on the case report forms.

6.0 TREATMENT OF SUBJECTS

6.1 Drug Preparation and Administration

6.1.1 Doublet Chemotherapy Preparation and Administration

Doublet chemotherapy of pemetrexed and carboplatin will be administered on Day 1 of each 21-day combination treatment cycle in Cycles 1 through 4 prior to L-DOS47 infusion.

6.1.1.1 Carboplatin

Carboplatin will be prepared as described in the drug package insert. It will be administered by intravenous infusion at a dose of AUC_6 mg/mL over 30 minutes.

6.1.1.2 Pemetrexed

Pemetrexed will be prepared as described in the drug package insert. It will be administered by intravenous infusion at a dose of 500 mg/m^2 over 10 minutes.

Pemetrexed Pre-medication:[12]

Vitamin Supplementation

Instruct patients to initiate folic acid 400 µg to 1000 µg orally once daily beginning 7 days before the first dose of pemetrexed. Continue folic acid during the full course of therapy and for 21 days after the last dose of pemetrexed.

Administer vitamin B12 1 mg intramuscularly 1 week prior to the first dose of pemetrexed and every 3 cycles thereafter. Subsequent vitamin B12 injections may be given the same day as treatment with pemetrexed.

Corticosteroids

Administer dexamethasone 4 mg orally twice daily the day before, the day of, and the day after pemetrexed administration.

6.1.2 L-DOS47 Preparation and Administration

L-DOS47 will be administered by intravenous infusion on Days 1, 8, and 15 of each 21-day combination treatment cycle in Cycles 1 through 4. Patients who have not progressed following the 4 cycles of combination treatment and who have not experienced unacceptable toxicity will have the opportunity to continue to receive additional cycles of L-DOS47 treatment for as long as there is clinical benefit and it is well-tolerated, in the opinion of the Investigator, until disease progression.

Patients who are unable to complete 4 cycles of L-DOS47 + pemetrexed/carboplatin combination treatment due to pemetrexed/carboplatin toxicity will have the opportunity to continue to receive additional cycles of L-DOS47 treatment following discontinuation of pemetrexed/carboplatin, for as long as there is clinical benefit and it is well-tolerated, in the opinion of the Investigator, until disease progression.

Simultaneous dosing of patients within a dosing cohort is prohibited. Patient dosing will be separated by at least 24 hours. This will allow for the assessment of possible infusion reactions and/or allergic reactions and enable communication between study centers.

L-DOS47 drug product is provided as a lyophilized cake in 3 mL stoppered and crimped Type I glass vials intended for reconstitution for i.v. infusion in normal saline (0.9% NaCl) solution with polysorbate 80. L-DOS47 should be stored at 2 - 8°C.

Complete instructions for L-DOS47 reconstitution and i.v. solution preparation can be found in the Pharmacy Manual. The starting dose of L-DOS47 in this trial is 0.59 µg/kg.

The L-DOS47 dose of each cycle will be calculated based on the patient's weight on Day 1 of that cycle. The dose will not be adjusted for body weight on Day 8 or 15 of the treatment cycles. Full weight-based doses will be used to treat obese patients.

L-DOS47 will be administered over a 30-minute period using an i.v. infusion pump. The start and end time of the infusion (actual clock time in 24 hour format) will be recorded on the eCRF. The rate of infusion may be decreased based on assessment of tolerability, and this will be reported as an adverse event (AE). Under no circumstances will the dose be administered in less than a 30-minute period. L-DOS47 infusion may be increased to 60 minutes in the event of a mild infusion reaction. The infusion bag for L-DOS47 must be used within 3 hours of preparation. If a patient exhibits signs and symptoms of anaphylaxis, he or she should be managed per local institutional guidelines. A central venous catheter is not required for infusion of L-DOS47; however, if the patient has a central venous catheter in place, it is recommended that it be used for the infusion.

For mild infusion reactions (transient flushing, rash or low grade fever < 38ºC or < 100.4ºF), anti-histamine, corticosteroids, and other medical intervention may be used as needed. If symptoms resolve within 30 minutes, the infusion may be resumed at a minimum 50% reduction in rate. If symptoms recur or worsen despite antihistamine and corticosteroids, the patient should be removed from the study. If a patient exhibits signs and symptoms of moderate to severe (anaphylaxis) infusion reactions such as bronchospasm with or without urticaria, edema/angioedema, hypotension, L-DOS47 infusion must be stopped immediately and they should be managed per local institutional guidelines.

Patients who experience mild infusion reactions manageable with anti-histamine and corticosteroids can be pre-medicated in the subsequent doses.

Patients must remain in the out-patient observation area for 2 hours after completion of the L-DOS47 infusion for observation prior to discharge.

6.1.3 L-DOS47 Dose Escalation Scheme

Dose escalation (Table 2) will be conducted with the specified increments as follows: initially, patients will receive increasing doses of L-DOS47 from 0.46 to 0.78 µg/kg (cohorts 1 to 2) using a modified Fibonacci schema[13]. Subsequent increments then followed a modified schedule of 100% (cohorts 3, 4 and 5), 50% (cohort 6), and 33% increments (cohort 7).

Table 2. L-DOS47 dose escalation scheme

Cohort	L-DOS47 Dose in µg/kg
-1*	0.46
1	0.59
2	0.78
3	1.5
4	3.0
5	6.0
6	9.0
7	12.0

*If the starting dose level results in DLT, patients will be treated at the -1 dose level.

6.1.4 Dose Escalation Rules

Dose escalation will proceed according to the following scheme based on DLTs occurring during the first cycle of treatment.

Table 3. Dose escalation rules

During the accelerated design phase (Cohorts 1 – 5)

No. of Patients with DLT at a Given Dose Level	**Escalation Decision Rule**
0 out of 1	**Enter patient(s) at the next dose level.**

1 out of 1	**Enter at least 2 more patients at this dose level.** • **If 0 of these 2 patients experiences DLT, proceed to the next dose level.** • **If 1 or more of this group suffer DLT, then dose escalation is stopped and this dose is declared the maximally administered dose. A total of 6 patients will be dosed at the next lowest dose level.**
1 out of 1	**Enter an additional 3 patients at this dose level, if the patient suffers a DLT as a result of one instance each of two unique grade 2 adverse events. Escalation decision will be based on standard design rules for these additional patients.**
≤ 1 out of 6 at highest dose level below the maximally administered dose	**This will be the Recommended Phase II Dose. At least 6 patients will be entered at this dose.**

During the standard design phase (Cohorts 6 and 7)

No. of Patients with DLT at a Given Dose Level	**Escalation Decision Rule**
0 out of 3	Enter patient(s) at the next dose level.
≥ 2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose level.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experiences DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped and this dose is declared the maximally administered dose. Three additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤ 1 out of 6 at highest dose level below the maximally administered dose	This will be the Recommended Phase II Dose. At least 6 patients will be entered at this dose.

6.1.5 Dose-limiting Toxicity

In the accelerated dose escalation phase of the study, Dose limiting toxicity (DLT) is defined as the occurrence of any of the following events (according to NCI CTCAE version 4.0) that are considered to be related to L-DOS47:

- **Hematologic adverse events ≥ grade 4**
- **Non-hematologic adverse events ≥ grade 3**
- **One instance each of any two unique grade 2 adverse events**

that occur within 21 days after commencing study drug treatment considered to be possibly, probably, or definitely related to L-DOS47 by the Investigator.

In the standard dose escalation phase, a DLT is defined as the occurrence of any of the following events (according to NCI CTCAE version 4.0):

- Hematologic adverse events ≥ grade 4
- Non-hematologic adverse events ≥ grade 3

that occur within 21 days after commencing study drug treatment considered to be possibly, probably, or definitely related to study drug treatment by the Investigator.

For the purpose of cohort evaluation, if a patient does not receive all of his/her scheduled L-DOS47 doses in Cycle 1 due to toxicity, this will be considered a DLT.

Patients experiencing a DLT during the first treatment cycle will be withdrawn from the study.

6.1.6 Maximum Tolerated Dose

The maximum tolerated dose (MTD)/recommended dose (RD) is defined as the highest dose level at which ≤ 1 of 6 patients experiences a dose limiting toxicity during the first treatment cycle.

If the MTD/RD is not confirmed following the evaluation of the final dosing cohort defined in the protocol, consideration will be given to test further cohorts. The same dosing schema will be used in determining these cohorts.

Once the MTD is defined, a confirmation cohort of approximately 10 patients will be enrolled at the MTD to determine the recommended Phase II doses for the combination treatment.

6.2 Dose Reductions/Modifications

Dose reductions/modifications for L-DOS47

If a patient experiences an AE meeting the definition of DLT (see Section 6.1.5), the patient will be withdrawn from the study and will not receive further doses of L-DOS47. Any AE occurring after the defined DLT criteria window will not be considered a DLT.

Table 4 below provides a list of L-DOS47 doses and dose reductions for each cohort. Criteria for dose reductions are described in Table 6.

Table 4. Dosing schedule for each treatment cycle (including dose reductions)

Cohort	Dose (µg/kg)	Dose Reduction (µg/kg)
1	0.59	0.46 (-1 dose)
2	0.78	0.59
3	1.5	0.78
4	3.0	1.5
5	6.0	3.0
6	9.0	6.0
7	12.0	9.0

To meet the criteria for retreatment, all toxicities considered by the Investigator to be related to therapy with L-DOS47 (except alopecia or anemia) must have resolved to ≤ Grade 2, or to a level considered acceptable by the Investigator, or to the patient's baseline values.

If the patient does not meet the retreatment criteria, the dose will be held and the patient should be reassessed weekly (or sooner if deemed clinically appropriate) for possibility of retreatment. If treatment is delayed for more than 14 days, the patient should be withdrawn from the study, unless discussed and agreed with the Medical Monitor.

Dose delay/modifications

Dose modification for subsequent cycles is required when any of the dose delay conditions in Table 5 or L-DOS47 toxicity criteria in Table 6 are met. Only one dose level reduction is allowed as outlined in Table 4.

In making the decision for dose modification, the worst case scenario should be used.

Table 5. Dose delay definitions

Dose delay	Occurrence	Action for L-DOS47
Up to 7 days	1st	None
Up to 7 days	2nd	Dose Reduction
Up to 7 days	3rd	Withdrawn[1]
8 to 14 days	1st	Dose Reduction
8 to 14 days	2nd	Withdrawn[1]

[1] The withdrawal of patients from study will be discussed with the Medical Monitor. A decision to not withdraw a patient must be agreed upon by the Sponsor and Medical Monitor, clinically supported and documented.

Table 6. Toxicity criteria for L-DOS47 dose modification

Toxicity	Grade	Occurrence	Relationship	Action for L-DOS47
Hematological				
Neutropenia				
	3 or 4	Any	Possible, probable, definite	None
	3 or 4	Any, prior delay of dosing	Possible, probable, definite	Dose Reduction
	3 or 4	2nd, prior dose reduction	Possible, probable, definite	Withdrawn[1]
Thrombocytopenia[2]				
	3 or 4	Any	Possible, probable, definite	None
	3 or 4	Any, prior delay of dosing	Possible, probable, definite	Dose Reduction
	3 or 4	2nd, prior dose reduction	Possible, probable, definite	Withdrawn[1]
Bleeding				
	1 or 2	1st	Possible, probable, definite	Dose Reduction
	1 or 2	Any, prior dose reduction	Possible, probable, definite	Withdrawn[1]
	3 or 4	1st	Possible, probable, definite	Withdrawn[1]
Non-Hematological				
	3	1st	Possible, probable, definite	Dose Reduction
	3	2nd, prior dose reduction	Possible, probable, definite	Withdrawn[1]
	4	1st	Possible, probable, definite	Withdrawn[1]

[1] The withdrawal of patients from study will be discussed with the Medical Monitor. A decision to not withdraw a patient must be agreed upon by the Sponsor and Medical Monitor, clinically supported and documented.
[2.] Without bleeding or platelet transfusion.

Dose reductions/modifications for pemetrexed and carboplatin:[14]
Doses will be reduced for hematological and other adverse events. Dose adjustments are to be made according to the system showing the greatest degree of toxicity, graded using the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE) (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf).

Any patient who requires a dose reduction will continue to receive a reduced dose for the remainder of the study. Any patient with 2 prior dose reductions who experiences a toxicity that would cause a third dose reduction must discontinue pemetrexed and carboplatin therapy.

Hematologic Toxicity

Dose adjustments at the start of a subsequent cycle of therapy will be based on platelet and neutrophils nadir (lowest value) counts from the preceding cycle of therapy. ANC must be $\geq 1.5 \times 10^9$/L and platelets $\geq 100 \times 10^9$/L prior to the start of any cycle. Treatment should be delayed to allow sufficient time for recovery. Upon recovery, if treatment is resumed, it should be according to the guidelines in Table 7 below.

Table 7. Dose adjustments for pemetrexed and carboplatin based on nadir hematologic values for preceding cycle

Platelets ($\times 10^9$/L) Nadir		ANC ($\times 10^9$/L) Nadir	Percent of Previous Dose
> 50	and	≥ 0.5	100%
> 50	and	< 0.5	75%
< 50	and	any	75%
< 50 + bleeding	and	any	50%
any	and	< 1.0 + fever of ≥ 38.5°C	75%
Recurrence of Grade 3 or 4 thrombocytopenia after 2 dose reductions		Recurrence of Grade 3 or 4 neutropenia after 2 dose reductions	Discontinue pemetrexed and carboplatin

Abbreviation: ANC = absolute neutrophil count.

Non-hematologic toxicity

In the event of diarrhea requiring hospitalization (or of at least Grade 3), treatment should be delayed until diarrhea has resolved before proceeding. Treatment with pemetrexed should be resumed at 75% of the previous dose level. The carboplatin should remain the same.

For other non-hematologic effects greater than or equal to Grade 3, with the exception of alopecia and mucositis, treatment must be delayed until resolution to less than or equal to the patient's baseline CTCAE grade before proceeding. Treatment should resume at 75% of the previous dose level if deemed appropriate by the treating physician. For Grade 3 or 4 transaminase elevations, the drug dose level should not be reduced.

Table 8. Dose modifications for pemetrexed and carboplatin for mucositis

	Dose for Next Cycle	
CTCAE Grade	**Pemetrexed**	**Carboplatin (AUC)**
Grade 0-2	100% of previous dose	100% of previous dose
Grade 3-4	50% of previous dose	100% of previous dose
Recurrence of Grade 3 or 4 after treatment at 2 dose reductions	Discontinue pemetrexed	Discontinue carboplatin

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events

Table 9. Dose modifications for pemetrexed and carboplatin in case of neurosensory toxicity

	Dose for Next Cycle	
CTCAE Grade	**Pemetrexed**	**Carboplatin (AUC)**
Grade 0-1	100% of previous dose	100% of previous dose
Grade 2	100% of previous dose	50% of previous dose
Grade 3-4 (or recurrence of Grade 2 after treatment at dose reduction for Carboplatin)	Discontinue pemetrexed	Discontinue carboplatin

Abbreviations: AUC = area under the curve; CTCAE = Common Terminology Criteria for Adverse Events

6.3 Concomitant Treatment

Chronic use of systemic steroids is prohibited. Acute use of systemic steroids is permitted. Use of steroid inhalers and topical steroids is permitted.

Any medication the patient takes other than the study treatment is considered a concomitant medication. All concomitant medications must be recorded on the eCRF. The following information must be recorded on the eCRF for each concomitant medication: generic name, route of administration, start date, stop date, dosage and indication. Any changes in the dosage or regimen of a concomitant medication must be recorded on the eCRF.

At the Screening Visit, patients will be asked what medications they have taken during the last 30 days. At each subsequent study visit, patients will be asked what concomitant medications they are currently taking.

6.3.1 Disallowed Medications

Other than the study treatments planned in this protocol, patients must not receive the following medications during the study: hormonal agents, other investigational drugs, systemic corticosteroids, and immunotherapy.

6.3.2 Allowed Medications

Radiotherapy may be given concomitantly for the control of bone pain; irradiated lesions will not be evaluable for response. Any medication which is considered necessary for the patient's welfare and which will not interfere with administration of the study treatments, may be given at the discretion of the Investigator.

6.4 Monitoring Subject Compliance

Study-related drugs will be administered only under the direction of the Investigator. Patients should attend scheduled clinic visits and comply with the protocol instructions. The Investigator will assess the patient for compliance with study procedures and visits and provide further advice to patients as necessary.

7.0 STUDY EVALUATIONS

7.1 Schedule of Study Evaluations

Study evaluations are summarized in the Table 10 and described in Sections 7.2 through 7.5.

Table 10. Schedule of study evaluations

	Pre-treatment Screening	**During Treatment L-DOS47 + Pemetrexed/Carboplatin[2] Cycles 1 through 4 Cycle Days (D)**				**End-of-Treatment Visit[3]**		**Additional Treatment Cycles[3]**	**Follow-up Visits**	
Procedures	**Days -28 to 0**	**D1**	**D8**	**D15**	**D21**	**Cycle 4 Day 21 7 (± 5) days post last dose**	**Early Termination (immediately)**	**L-DOS47 only[19]**	**30 Days post last dose**	**Thereafter, every 30 days[*] (± 7 days) or every 6 weeks[**] (± 7 days)**
Informed Consent[1]	X									
Inclusion/exclusion criteria	X	X								
Demographics	X									
Weight	X	X predose						X D1 predose		
Medical history	X									
Physical examination	X	X predose	X predose			X	X	X D1, 8, 15 predose		
Performance status (ECOG)	X	X				X	X	X D1		

	Pre-treatment Screening	**During Treatment L-DOS47 + Pemetrexed/Carboplatin[2] Cycles 1 through 4 Cycle Days (D)**				**End-of-Treatment Visit[3]**		**Additional Treatment Cycles[3]**	**Follow-up Visits**	
Procedures	**Days -28 to 0**	**D1**	**D8**	**D15**	**D21**	**Cycle 4 Day 21 7 (± 5) days post last dose**	**Early Termination (immediately)**	**L-DOS47 only[19]**	**30 Days post last dose**	**Thereafter, every 30 days* (± 7 days) or every 6 weeks** (± 7 days)**
Radiologic examination[6] and tumor assessment	X	X				X (if > 6 wks post last scan)	X (if > 6 wks post last scan)	X D1 every other cycle	X	X
Historic biopsy sample (if available)	X									
Tumor antigen assessment (CEACAM6)[7]		X predose Cycle 2 only	X predose Cycle 4 only			X (only if not done on C4D8)	X (only if not done on C4D8)			
Vital Signs (temp/HR/BP/RR/pulse oximetry)[8,20]	X	X pre- & post-dose	X pre- & post-dose	X		X	X	X D1, 8, 15		
Electrocardiogram[9, 20]	X	X pre- & post-dose	X pre- & post-dose			X	X	X D1 and 8 Predose & postdose (optional [10])		

	Pre-treatment Screening	**During Treatment L-DOS47 + Pemetrexed/Carboplatin[2] Cycles 1 through 4 Cycle Days (D)**				**End-of-Treatment Visit[3]**		**Additional Treatment Cycles[3]**	**Follow-up Visits**	
Procedures	**Days -28 to 0**	**D1**	**D8**	**D15**	**D21**	**Cycle 4 Day 21 7 (± 5) days post last dose**	**Early Termination (immediately)**	**L-DOS47 only[19]**	**30 Days post last dose**	**Thereafter, every 30 days* (± 7 days) or every 6 weeks** (± 7 days)**
Clinical lab tests[4] Hematology Chemistry Coagulation	X	X predose	X predose			X	X	X D1, 8, 15 predose		
Urinalysis[5]	X	X predose	X predose			X	X	X D 1, 8, 15 predose		
Pregnancy test[11]	X	X predose				X	X	X D1 predose		
L-DOS47 administration[12]		X	X	X				X D1, 8, 15		
Pemetrexed/Carboplatin administration[13]		X								
Plasma PK sampling[14,20]		X	X							

	Pre-treatment Screening	**During Treatment L-DOS47 + Pemetrexed/Carboplatin[2] Cycles 1 through 4 Cycle Days (D)**				**End-of-Treatment Visit[3]**		**Additional Treatment Cycles[3]**	**Follow-up Visits**	
Procedures	**Days -28 to 0**	**D1**	**D8**	**D15**	**D21**	**Cycle 4 Day 21 7 (± 5) days post last dose**	**Early Termination (immediately)**	**L-DOS47 only[19]**	**30 Days post last dose**	**Thereafter, every 30 days* (± 7 days) or every 6 weeks** (± 7 days)**
Serum collection for anti-L-DOS47 antibody testing[15]		X predose	X predose C1 only			X	X	X Day 1 predose	X	
Concomitant medications	X	X[16] predose	X[16] predose			X	X	X D1, 8, 15 predose	X	
Adverse Events		X[17]	X[17]	X[17]	X[17]	X	X	X D1, 8, 15 predose and postdose	X	
Disease progression and Survival[18]										X

ECOG: Eastern Cooperative Oncology Group; Temp: Temperature; HR; Heart rate; BP: Blood pressure; RR: Respiratory rate; PK: Pharmacokinetic; ECG: Electrocardiogram; CT: Computed tomography; MRI: Magnetic resonance imaging

1 Informed consent will be obtained before any experimental procedure or test is performed.

2 All patients will be administered up to four cycles of L-DOS47 during the study treatment period. Treatment cycles will be repeated for patients who tolerate the previous treatment cycle of L-DOS47 and show no clinical signs of progression of disease.

3 The End-of-Treatment Visit will be performed one time for all patients who discontinue the study at or before the end of Cycle 4. For patients who continue to receive additional cycles of L-DOS47 (i.e., Cycle 5 and beyond), this visit will be performed twice: (i) after the completion of 4 cycles; (ii) at the time of discontinuation from the study. Note: All patients who are withdrawn from the study will complete the End-of-Treatment Visit immediately at the time of withdrawal.

4 The corresponding procedures will be performed on the day specified for each L-DOS47 cycle:
Hematology: CBC with differential and platelet count;
Serum chemistry: albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), urea, calcium, bicarbonate, chloride, creatinine (by Cockcroft-Gault formula), globulin (serum globulin: total protein minus serum albumin), glucose, phosphate, potassium, sodium, magnesium, total bilirubin, total protein.
Coagulation: prothrombin time/international normalized ratio (PT/INR), activated partial thromboplastin time (aPTT).

5 Urinalysis: bilirubin, glucose, ketones, occult blood, protein.

6 Radiologic examinations will be performed during screening, unless results from appropriate scans performed within 28 days prior to the first dose of study drug are available and every other treatment cycle (i.e., every 6 weeks) until disease progression; an MRI may be conducted only in exceptional cases. Radiologic examination is to be repeated at the End of Treatment Visit if > 6 weeks have passed since the last evaluation.

7 Tumor antigen (CEACAM6) assessment: blood samples will be drawn (predose [0 hours]) on Day 1 (predose [0 hours]) of Cycle 2 and on Day 8 of Cycle 4 or the End of Treatment Visit (whichever occurs first).

8 Vital signs (temperature, heart rate, blood pressure, respiratory rate and oxygen saturation [pulse oximetry]) will be assessed prior to pemetrexed/carboplatin administration on Day 1 of the cycle; on treatment days in which L-DOS47 will be administered (Days 1, 8, and 15), vital signs will also be serially recorded relative to start of L-DOS47 infusion as follows: Cycle 1, Days 1 and 8: predose and 10 and 20 minutes (during infusion), and 30 minutes (prior to end of infusion) and 1, 2, and 4 hours postdose; Cycle 2, Days 1 and 8: predose and 15 minutes (during infusion), and 30 minutes (prior to end of infusion). Cycle 2, Day 1 at 1 and 2 hours postdose; Cycle 2, Day 8 at 1, 2, and 4 hours postdose; Cycles 3 and 4, Days 1 and 8: predose and 30 minutes (prior to end of infusion). All cycles, Day 15: 15 minutes (during infusion), and 30 minutes (prior to end of infusion).

9 Serial 12-lead ECG measurements will be recorded on Days 1 and 8 of each cycle as follows: predose and at 1 and 1.5 hours postdose.

10 For additional cycles, all ECG recordings are optional.

11 In women of childbearing potential, serum ß-HCG tests will be conducted at Screening and at the End-of-Treatment/Early Termination Visit. Urine ß-HCG tests will be conducted on Day 1 of each treatment cycle.

12 L-DOS47 will be administered on Days 1, 8, and 15 of each treatment cycle. Treatment with L-DOS47 may continue beyond four cycles for as long as the patient is receiving sustained clinical benefit and it is well tolerated, in the opinion of the Investigator, until disease progression.

13 Pemetrexed/carboplatin will be administered according to standard prescribing information on the first day of treatment cycles 1 through 4, prior to L-DOS47 administration.

14 Serial blood samples (plasma) for L-DOS47 PK will be collected from all patients as follows: Cycle 1, Days 1 and 8: predose and serially postdose (time relative to the start of infusion) at 15 (during infusion), 30 (prior to end of infusion)*, 45 minutes* and 1*, 1.5, 2, 3, 4, 24, and 48 hours postdose; Cycles 2 and 4, Day 8: predose and serially postdose (time relative to the start of infusion) at 15 (during infusion), 30 (prior to end of infusion)*, 45 minutes* and 1*, 1.5, 2, 3, 4, and 24 hours postdose; Cycle 2, Day 1; Cycle 3, Days 1 and 8; Cycle 4, Day 1: predose and 30 minutes* postdose (time relative to the start of infusion, to be collected just prior to end of infusion). * If the L-DOS47 infusion time is increased from 30 minutes to 60 minutes in the event of a mild infusion reaction, there will be no change in the PK sampling timepoints, which are all relative to the start of L-DOS47 infusion. PK samples collected at 30 minutes and 45 minutes will be considered during infusion samples and

PK sample collected at 60 minutes (1 hour) will be a prior to end of infusion sample. All other timepoints remain the same. Also refer to Section 8.3 and Table 14 for PK timepoints.

15 Serum samples will be collected (2 mL/ in SST tubes) for anti-L-DOS47 antibody testing on Cycle 1 (Day 1 [predose; baseline] and Day 8 [predose]), Cycles 2 through 4 (Day 1 [predose]), all additional cycles (i.e., Cycle 5 and beyond, Day 1 [predose], at the End-of-Treatment Visit or Early Termination Visit, and 30 days after the last dose.

16 Concomitant medications will be recorded predose on Days 1 and 8 of each cycle

17 Adverse events (AE) will be recorded predose and postdose on Days 1, 8, and 15 of each cycle, and the Cycle 4 End-of-Treatment Visit. On non-visit days, AE will be monitored by telephone contact. Adverse event monitoring on Day 21 need only occur under the circumstance that the patient is coming off study and the next cycle is not being initiated.

18 Patients will be followed to collect data pertaining to progression and survival. Survival data* will be captured by telephone call every 30 days (± 7 days) until death. Follow-up for progression** will be conducted by radiologic assessments (CT scans of chest, abdomen and pelvis, or as appropriate per the Investigator) every 6 weeks (± 7 days) until one of the following occurs: disease progression, patient initiates non-study cancer treatment, patient withdraws consent, or patient is lost-to-follow-up.

19 Cycle 5, Day 1 assessments may not need to be repeated if the end of Cycle 4 evaluations are performed within 7 days prior to Day 1 of Cycle 5.

20 ECG/Vital signs/PK time window table presented below define an acceptable lapse in assessment/sample collection.

ECG/Vital signs/PK time window [a]

	ECG	Vital signs	PK
During infusion	± 5 min	± 5 min	± 5 min
Post infusion	± 5 min	± 5 min	± 5 min [b,c]

a. All timepoints are relative to the start of L-DOS47 infusion
b. If the L-DOS47 infusion time is increased from 30 minutes to 60 minutes in the event of a mild infusion reaction, there will be no change in the PK sampling timepoints. The PK sample collected at 60 minutes (1 hour) will be the end of infusion sample. All other timepoints remain the same.
c. For PK samples collected at 24 and 48 hours timepoints, the window will be ± 30 min.

7.2 Pre-treatment

To be conducted within 28 days prior to first dose of study treatment (Days -28 to 0).
The following assessments will be performed and measurements recorded after the patient has read and signed the informed consent:

- Verify conformance with entry criteria
- Demographics
- Weight
- Record medical history
- Physical examination
- ECOG performance status
- Radiologic examination, unless results from appropriate scans performed within 28 days of the first dose of study drug are available
- Historic biopsy sample (if available)
- Vital signs (temperature, heart rate, blood pressure, respiratory rate, oxygen requirement [pulse oximetry])
- 12-lead Electrocardiogram (ECG)
- Hematology, blood chemistry and coagulation
- Urinalysis
- Serum pregnancy test, for women of childbearing potential
- Concomitant medication

7.3 During Treatment

Cycles 1 through 4
Prior to L-DOS47 Dosing
Days 1 and 8
The following assessments will be performed for each treatment cycle on Days 1 and 8 (unless specified otherwise) and measurements recorded before dosing:

- Verify conformance with entry criteria (Cycle 1, Day 1 only)
- Weight (Day 1 of each cycle)
- Physical examination
- ECOG performance status (Day 1 of each cycle)
- Radiologic examination after the completion of Cycle 2 and every 6 weeks thereafter
- Tumor antigen assessment: blood draws on Day 1 (predose [0 hours]) of Cycle 2 and Day 8 of Cycle 4 (or performed at the End-of-Treatment/Early Termination Visit-depending on which occurs first).
- Vital signs (temperature, heart rate, blood pressure, respiratory rate, oxygen requirement [pulse oximetry])

- 12-lead ECG
- Hematology, blood chemistry and coagulation
- Urinalysis
- Urine pregnancy test (Day 1 of each cycle)
- Plasma PK sampling
- Serum collection for anti-L-DOS47 antibody testing (Cycle 1, Day 1 (baseline) and Day 8; Cycles 2 through 4, Day 1 only)
- Concomitant medications
- Adverse event monitoring

Dosing

- Administration of pemetrexed/carboplatin (Day 1 of Cycles 1 through 4)
- Administration of L-DOS47 (Days 1, 8, and 15 of Cycles 1 through 4)

During L-DOS47 Dosing

The following assessments will be performed and measurements recorded during dosing:
PK/Vital signs/ECG timepoint assessments will be obtained in the following order:

1. Vital signs
2. 12-lead ECG
3. PK blood sample
4. Any other scheduled or unscheduled measurements at that timepoint

Serial recordings and sampling will be timed relative to the start of infusion:

- Vital signs (temperature, heart rate, blood pressure, respiratory rate, oxygen requirement [pulse oximetry]) as follows (relative to start of infusion):
    - Cycle 1, Days 1 and 8: 10 and 20 minutes (during infusion) and 30 minutes (prior to end of infusion)
    - Cycle 2, Days 1 and 8: 15 minutes (during infusion) and 30 minutes (prior to end of infusion)
    - Cycles 3 and 4, Days 1 and 8: 30 minutes (prior to end of infusion).
    - All cycles, Day 15: 15 minutes (during infusion) and 30 minutes (prior to end of infusion)
- Plasma PK sampling as follows (time relative to start of infusion) (also refer to Section 8.3 for PK timepoints):
    - Cycle 1, Days 1 and 8: 15 (during infusion) and 30 minutes* (prior to end of infusion)
    - Cycles 2 and 4, Day 8: 15 (during infusion) and 30 minutes * (prior to end of infusion)
    - Cycle 2, Day 1; Cycle 3, Days 1 and 8; Cycle 4, Day 1: 30 minutes * (prior to end of infusion)

* If the L-DOS47 infusion time is increased from 30 minutes to 60 minutes in the event of a mild infusion reaction, there will be no change in the PK sampling timepoints, which are all relative to the start of L-DOS47 infusion. PK samples collected at 30 minutes and 45 minutes will be considered during infusion samples and PK sample collected at 60 minutes (1 hour) will be a prior to end of infusion sample. All other timepoints remain the same.

Post L-DOS47 Dosing

The following assessments will be performed and measurements recorded after dosing:

- Vital signs (temperature, heart rate, blood pressure, respiratory rate, oxygen requirement [pulse oximetry]) as follows (relative to start of infusion):
  - Cycle 1 Days 1 and 8: 1, 2, and 4 hours postdose
  - Cycle 2 Day 1: 1 and 2 hours postdose
  - Cycle 2 Day 8: 1, 2, and 4 hours postdose
- 12-lead ECG: 1 and 1.5 hours postdose (Days 1 and 8 of each cycle)
- Plasma PK sampling as follows (time relative to start of infusion) (also refer to Section 8.3 for PK timepoints):
  - Cycle 1, Days 1 and 8: 45 minutes* and 1*, 1.5 , 2, 3, 4, 24 and 48 hours postdose
  - Cycles 2 and 4, Day 8: 45 minutes* and 1*, 1.5, 2, 3 , 4 and 24 hours postdose

* If the L-DOS47 infusion time is increased from 30 minutes to 60 minutes in the event of a mild infusion reaction, there will be no change in the PK sampling timepoints, which are all relative to the start of L-DOS47 infusion. PK samples collected at 30 minutes and 45 minutes will be considered during infusion samples and PK sample collected at 60 minutes (1 hour) will be a prior to end of infusion sample. All other timepoints remain the same.

- Adverse event monitoring (Days 1, 8, 15 and 21 of each cycle), on non-visit days AEs will be monitored by telephone contact

Day 15

Prior to L-DOS47 Dosing

- Adverse event monitoring
- Vital signs

Dosing

- Administration of L-DOS47
- Vital signs

Post L-DOS47 Dosing

- Adverse event monitoring
- Vital signs

Day 21

- Adverse event monitoring by telephone contact – to be done only if the patient is coming off study and the next cycle is not being initiated

Additional Treatment Cycles

After completion of four cycles of L-DOS47, patients may continue to receive L-DOS47 for as long as there is sustained clinical benefit and it is well tolerated, in the opinion of the Investigator, until disease progression.

Cycle 5, Day 1 assessments may not need to be repeated if the end of Cycle 4 evaluations are performed within 7 days prior to Day 1 of Cycle 5.

For those patients who continue to receive additional cycles of L-DOS47, the following assessments will be performed on Days 1, 8, and 15 predose during each treatment cycle (unless specified otherwise) and measurements recorded:

- Weight (Day 1 of each cycle)
- Physical examination (Days 1, 8, and 15 of each cycle)
- ECOG performance status (Day 1 of each cycle)
- Radiological exam (Day 1 of every other cycle, i.e., every 6 weeks)
- Vital signs [temperature, heart rate, blood pressure, respiratory rate, oxygen requirement (pulse oximetry)] (Days 1, 8, and 15 of each cycle)
- Optional 12-lead ECG (predose and postdose): Days 1 and 8 of each cycle
- Hematology, blood chemistry and coagulation (Days 1, 8, and 15 of each cycle)
- Serum collection for anti-L-DOS47 antibody testing (Day 1 only)
- Urinalysis (Days 1, 8, and 15 of each cycle)
- Urine pregnancy test, for women of childbearing potential (Day 1 of each cycle)
- Concomitant medications (Days 1, 8, and 15 of each cycle)
- Adverse event monitoring (Days 1, 8 and 15 pre- and post-dose)

7.4 Off-Study

For the initial four cycles, The End-of-Treatment Visit will be Day 21 of Cycle 4 (patients who complete all four treatment cycles) or will be the Early Termination visit (for patients withdrawn from the study), whichever occurs first. All patients will be required to complete the End-of-Treatment Visit.

Patients who are continuing beyond the initial four cycles, (i.e., completed the initial four cycles), will complete the End-of-Treatment Visit on Day 21 of Cycle 4 and the next visit will be

Cycle 5, Day 1. Patients continuing beyond Cycle 4 will complete the End-of-Treatment Visit again at the time of withdrawal from the study.

All patients who are withdrawn from the study will complete the End-of-Treatment Visit immediately at the time of withdrawal.
The following assessments will be performed and measurements recorded:

- Physical examination
- ECOG performance status
- Radiologic examination (if > 6 weeks have passed since the last evaluation)
- Tumor antigen assessment: perform only if not done on Day 8 of Cycle 4
- Vital signs (temperature, heart rate, blood pressure, respiratory rate, oxygen requirement [pulse oximetry])
- 12-lead ECG
- Hematology, blood chemistry and coagulation
- Urinalysis
- Serum collection for anti-L-DOS47 antibody testing
- Serum pregnancy test, for women of childbearing potential
- Concomitant medications
- Adverse event monitoring

7.5 Long-Term Follow-up

Follow-up assessments will be conducted after the End-of-Treatment Visit. Long-term follow-up for disease progression will be conducted by radiologic assessments every 6 weeks (± 7 days) until one of the following occurs: disease progression, patient initiates non-study cancer treatment, patient withdraws consent or becomes lost-to-follow-up. Survival data will be captured by telephone call every 30 days (± 7 days) and patients will be followed until death.

8.0 STUDY ASSESSMENTS

8.1 Safety Assessments

8.1.1 Safety Analysis

Safety data will be tabulated for all patients and include vital signs, laboratory parameters, and adverse events.

8.1.2 Reporting of Adverse Events

8.1.2.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with the treatment. An adverse event can be any unfavorable and unintended sign (including a laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

The adverse event reporting period will commence after the initial dosing of pemetrexed premedication. If an AE occurs before the first dose of study drug it will be considered a non-treatment emergent AE. At each evaluation patients should be interviewed in a non-directed manner to elicit potential adverse reactions from the patient. The occurrence of an adverse event will be based on changes in the patient's physical examination, laboratory results, and/or signs and symptoms.

All adverse events (except grade 1 and 2 laboratory abnormalities that do not require an intervention), regardless of causal relationship, are to be recorded in the case report form and source documentation. The Investigator must determine the intensity of any adverse events according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (see http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf) and their causal relationship. Those AEs not covered by these criteria will be graded as follows:

1. Mild: Discomfort noticed, but no disruption of normal daily activity. Prescription drug not ordinarily needed for relief of symptom but may be given because of personality of patient.

2. Moderate: Discomfort sufficient to reduce or affect normal daily activity. Patient is able to continue in study; treatment for symptom may be needed.

3. Severe: Incapacitating, severe discomfort with inability to work or to perform normal daily activity. Severity may cause cessation of treatment with test drug; treatment for symptom may be given and/or patient hospitalized.

4. Life-Threatening: Symptom(s) place the patient at immediate risk of death from the reaction as it occurred; it does not include a reaction that had it occurred in a more serious from, might have caused death.

5. Fatal: Event caused the death of the patient.

Adverse events will be followed until resolution or stabilization while the patient remains on-study. Once the patient is removed from study, events thought to be related to the study medication will be followed until resolution or stabilization, unless, in the Investigator's opinion the event is unlikely to resolve due to the patient's underlying disease, or until the patient starts a new treatment regimen or the patient is lost to follow-up.

8.1.2.2 Attribution Definitions

An adverse event is considered to be associated with the use of the Investigational agent if the attribution is determined as possible, probable or definite. Attribution of AEs will be recorded in the CRF as:

- Unrelated: The AE is clearly NOT related to the study treatment.
- Unlikely: The AE is doubtfully related to the study treatment.
- Possible: The AE may be related to the study treatment.
- Probable: The AE is likely related to the study treatment.
- Definite: The AE is clearly related to the study treatment.

8.1.2.3 Definition of an Unexpected Adverse Event

An unexpected adverse event is defined as any adverse drug experience, the specificity or severity of which is not consistent with the current Investigator Brochure; or, if an Investigator Brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in this protocol or in the regulatory agency study authorization application.

Unexpected, as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the Investigator Brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

8.1.2.4 Serious Adverse Event (SAE)

A serious adverse event is defined as any untoward medical occurrence that at any dose:

1. Results in death,

2. Is life-threatening (i.e., the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe),

3. Requires in-patient hospitalization or prolongation of existing hospitalization excluding that for pain management, disease staging/re-staging procedures, or catheter placement unless associated with other serious events,

4. Results in persistent or significant disability/incapacity, or

5. Is a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based on appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

8.1.2.5 Pregnancy

Any pregnancy diagnosed during the study, or that occurs within 30 days after stopping study medication, must be reported immediately to the Investigator. Pregnancy, in and of itself, is not regarded as an adverse event, unless there is suspicion that study medication may have interfered with the effectiveness of a contraceptive medication. If the patient becomes pregnant while on-study, the study drug should be immediately discontinued. Pregnancy information about a female patient or a female partner of a male patient should be reported immediately from the time the Investigator first becomes aware of a pregnancy or its outcome. This will be performed by the Investigator completing a Pregnancy Form and faxing it [in the US] to Theradex® at (609) 799-1567; contact the Theradex® Safety Desk (see Section 8.1.2.6) for the Pregnancy Form.

Any pregnancy complication, spontaneous abortion, elective termination of a pregnancy for medical reasons, outcome of stillbirth, congenital anomaly/birth defect, or serious adverse event in the mother will be recorded as an SAE and will be reported as described in Section 8.1.2.6.

8.1.2.6 Reporting of Serious Adverse Events

Adverse events classified as serious require expeditious handling and reporting to Theradex® to comply with regulatory requirements.

The serious adverse event reporting period will commence after the initial dose of pemetrexed premedication.

For any serious adverse event (SAE) that occurs while a patient is on-study; within 30 days of the last study drug administration, regardless of any opinion as to the relationship of the SAE to the study drug; or if any SAE that the Investigator feels is related to the study drug occurs later than 30 days after the last study drug administration, the Theradex® Safety Desk must be notified

immediately (within 24 hours of becoming aware of the event) by fax, email or telephone. Notification by email is preferred. The fax and telephone numbers and the email address listed below may be used during both business and non-business hours. During non-business hours a recorded message will provide the caller with the contact information for the on-call monitor.

All SAEs require that a Serious Adverse Event Report Form be completed and forwarded either via facsimile or as a PDF via email to Theradex® at the fax number or email listed below within 24 hours of becoming aware of the event.

In the USA, SAEs will be reported to:

Theradex® Safety Desk
Telephone: (609) 799-7580
Fax: (609) 799-1567
Email: SafetyDeskUS@Theradex.com

8.2 Efficacy Assessments

Although response is not the primary endpoint of this study, patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be evaluated every 6 weeks. In addition to a baseline scan, confirmatory scans will also be obtained 4 weeks following initial documentation of an objective response.

8.2.1 Definitions

Response and progression will be evaluated in this study using the international criteria (version 1.1) proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [Eur J Cancer. 45 (2009) 228-247].[15] Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST 1.1 criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

8.2.1.1 Measurable Disease

Measurable disease is defined by the presence of at least one measurable lesion. Measurable lesions are defined as those that can be accurately measured in at least one dimension [longest diameter (LD) in the plane of measurement to be recorded] with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest x-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness no greater than 5 mm).

8.2.1.2 Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) are considered non-measurable disease. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses/abdominal organomegaly identified by physical exam and not followed by CT or MRI.

Bone lesions, cystic lesions and lesions previously treated with local therapy must be considered as follows:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques (i.e., CT or MRI) can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

8.2.1.3 Target Lesions

All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference by which to characterize the objective tumor response.

8.2.1.4 Lymph Node Assessment

For lymph nodes, measurements should be made of the short axis, which is defined as perpendicular to the LD of node assessed in the plane of measurement:

- Target lesion if short axis ≥ 15 mm
- Non-target lesion if short axis is ≥ 10 but < 15 mm
- Normal if short axis < 10 mm

For baseline, add the actual short axis measurement to the sum of LD of non-nodal lesions.

8.2.1.5 Non-target Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression." In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

8.2.2 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

Chest x-ray. Chest CT is preferred over chest x-ray, particularly when progression is an important endpoint. Lesions on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is acceptable in certain situations (e.g., for body scans).

Ultrasound (US). US should not be used to measure tumor lesions. US examinations cannot be reproduced in their entirety for independent review at a later date because they are operator dependent. If new lesions are identified by US, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers. Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. *Because tumor markers are disease specific (e.g., PSA response in recurrent prostate cancer and CA-125 in recurrent ovarian cancer) instructions for their measurement should be incorporated into protocols on a disease specific basis.*

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). *When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors) the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease (SD) in order to differentiate between response (or SD) and progressive disease (PD).*

8.2.3 Response Criteria

8.2.3.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

8.2.3.1.1 Assessment of Target Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline exam), even if the nodes regress to below 10 mm on study. In order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

8.2.3.1.2 Target Lesions that Become "too small to measure"

All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). If it is the opinion of the radiologist that the lesion has disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned.

8.2.3.1.3 Lesions that Split or Coalesce on Treatment

When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter should be the maximal longest diameter for the 'coalesced lesion.'

8.2.3.2 Evaluation of Non-target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/Non-PD:	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions. (The appearance of one or more new lesions is also considered progression.) To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation.

8.2.3.3 New Lesions

The finding of a new lesion should be unequivocal (i.e., not attributed to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor, such as a 'new' healing bone lesion). A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. If a new lesion is equivocal, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm this is definitely a new lesion, then progression should be declared using the date of the initial scan.

8.2.3.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best overall response assignment will depend on findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study, it may also require confirmatory measurement. Specifically, in non-randomized trials where

response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "best overall response."

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 11 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline. When patients have non-measurable disease, Table 12 should be used.

Table 11. Timepoint response: Patients with target (+/- non-target) disease

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR / non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
CR=complete response, PR=partial response, SD=stable disease PD=progressive disease, NE=inevaluable			

Table 12. Timepoint response: Patients with non-target disease only

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR / non-PD	No	Non-CR / non-PD*
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR=complete response; PD=progressive disease; NE=inevaluable * Non-CR/non-PD is preferred over SD for non-target disease		

Best response determination for studies where confirmation of CR or PR is required: Complete or partial responses may be claimed only if the criteria for each are confirmed by a repeat assessment at least 4 weeks later. In this circumstance, the best overall response can be interpreted as in Table 13.

Table 13. Best overall response when confirmation of CR and PR required

Overall response First timepoint	Overall response Subsequent timepoint	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR*
CR	SD	SD provided minimum criteria for SD duration met, otherwise PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease; NE=inevaluable

* If CR is truly met at first timepoint, then any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in the fact patient had PR, not CR, at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

8.2.4 Confirmatory Measurement/Duration of Response

8.2.4.1 Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 42 days

8.2.4.2 Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

8.2.4.3 Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

8.2.5 Clinical Benefit

Clinical benefit will be calculated as the percentage of patients achieving complete response, partial response, and stable disease. For patients to be evaluable for stable disease, the duration of stable disease must be at least 42 days from the first dose of study treatment.

8.3 Pharmacokinetics

Plasma samples for pharmacokinetics will be collected as follows:

Cycle 1, Days 1 and 8: predose and serially postdose (time relative to the start of infusion) at 15 (during infusion), 30 (prior to end of infusion)*, 45 minutes* and 1*, 1.5, 2, 3, 4, 24, and 48 hours postdose Cycles 2 and 4, Day 8: predose and serially postdose (time relative to the start of infusion) at 15 (during infusion), 30 (prior to end of infusion) *, 45 minutes* and 1*, 1.5, 2, 3, 4, and 24 hours postdose; Cycle 2, Day 1; Cycle 3, Days 1 and 8; Cycle 4, Day 1: predose and 30 minutes* postdose (time relative to the start of infusion, to be collected just prior to end of infusion)

Cycles 2 and 4, Day 8: predose and serially postdose (time relative to the start of infusion) at 15 (during infusion), 30 (prior to end of infusion)*, 45 minutes* and 1*, 1.5, 2, 3, 4, 6, and 24 hours postdose; Cycle 2, Day 1; Cycle 3, Days 1 and 8; Cycle 4, Day 1: predose and 30 minutes * postdose (time relative to the start of infusion, to be collected just prior to end of infusion).

* If the L-DOS47 infusion time is increased from 30 minutes to 60 minutes in the event of a mild infusion reaction, there will be no change in the PK sampling timepoints, which are all relative to the start of L-DOS47 infusion. PK samples collected at 30 minutes and 45 minutes will be considered during infusion samples and PK sample collected at 60 minutes (1 hour) will be a prior to end of infusion sample. All other timepoints remain the same. [see Table 14].

Table 14. L-DOS47 plasma pharmacokinetic sampling schedule

Protocol Scheduled Day	Protocol Scheduled Timepoint[a]
Cycle 1, Day 1 and Cycle 1, Day 8	Predose
	During infusion: 15 minutes 30 minutes (prior to end of infusion) [b]
	Post infusion: [c] 45 minutes [b] 1 hour [b] 1.5 hours 2 hours 3 hours 4 hours 24 hours (Day 2) 48 hours (Day 3)
Cycle 2, Day 8 Cycle 4, Day 8	Predose
	During infusion: 15 minutes 30 minutes (prior to end of infusion) [b]
	Post infusion: [c] 45 minutes [b] 1 hour [b] 1.5 hours 2 hours 3 hours 4 hours 24 hours (Day 9)
Cycle 2, Day 1 Cycle 3, Day 1 Cycle 3, Day 8 Cycle 4, Day 1	Predose
	During infusion: 30 minutes (prior to end of infusion) [b]

a. Time windows for PK samples collected during infusion and post infusion are ± 5 min, exception include PK samples collected at 24 and 48 hours (post infusion) timepoints, the time window for these timepoints will be ± 30 min.
b. If the L-DOS47 infusion time is increased from 30 minutes to 60 minutes in the event of a mild infusion reaction, there will be no change in the PK sampling timepoints, which are all relative to the start of L-DOS47 infusion. PK samples collected at 30 minutes and 45 minutes will be considered during infusion samples and PK sample collected at 60 minutes (1 hour) will be a prior to end of infusion sample. All other timepoints remain the same.
c. Time relative to start of infusion

8.4 Immunogenicity

The immunogenicity of L-DOS47 will be evaluated from serum samples collected on Cycle 1, Day 1 (predose; baseline) and Day 8 (predose), Cycles 2 through 4 (Day 1, predose), all additional cycles (i.e., Cycle 5 and beyond, Day 1 (predose), at the end of treatment or early termination visit, and at the follow-up visit (30 days after the last dose).

9.0 STATISTICS

Demographic data will be displayed and descriptive summary statistics will be used to describe the study population (e.g., ranges, mean and medians of age, and weight; numbers of males and females; description of baseline performance status characteristics; tabulation of tumor types and histology).

Safety data will be tabulated for all patients who receive any amount of study treatment. These data will include laboratory parameters, adverse events, and cardiographic values. The tabulation of laboratory parameters will indicate the normal ranges for each parameter. Each value will be classified as falling above, below, or within the normal range.

Adverse events will be tabulated by body system, severity and relation to treatment. For the purposes of presentation, groups will be arranged by decreasing frequency of adverse events.

Efficacy data will be tabulated. The best overall response rate, defined using RECIST 1.1, will be summarized for efficacy-evaluable patients. The percentage of patients in each of the best overall response categories will be presented. The overall response rate will be calculated as the proportion of patients with responsive disease (CR and PR). Clinical benefit will be calculated as the percentage of patients achieving complete response, partial response, and stable disease. For patients to be evaluable for stable disease, the duration of stable disease must be at least 42 days from the first dose of study treatment. Clinical benefit data from all cohorts will be displayed in a waterfall plot.

Pharmacokinetic parameters will be determined from L-DOS47 concentrations using non-compartmental methods (WinNonLin®). L-DOS47 PK parameters to be calculated (if adequate data are available for estimation) will include maximum concentration (C_{max}), time of C_{max} (T_{max}), applicable area under the curve (AUC) parameters, terminal half-life ($t½$), systemic clearance (CL), volumes of distribution (V_z) and volume of distribution at steady state (V_{ss}) and urinary excretion parameters. The concentrations and PK parameters will be summarized using descriptive statistics (n, mean, standard deviation, percent coefficient of variation, geometric mean, median, minimum and maximum).

Immunogenicity data will be tabulated. The concentration of anti-L-DOS47 antibodies will be evaluated using descriptive statistics.

10.0 QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

10.1 Monitoring of the Study and Regulatory Compliance

The project manager, or designee, will make an initiation site visit to each institution to review the protocol and its requirements with the Investigator(s), inspect the drug storage area, fully inform the Investigator of his/her responsibilities and the procedures for assuring adequate and correct documentation. During the initiation site visit the case report forms (CRFs) will be reviewed. Other pertinent study materials will also be reviewed with the Investigator's research staff. During the course of the study, the monitor will make regular site visits in order to review protocol compliance, examine CRFs and individual subject's medical records and assure that the study is being conducted according to pertinent regulatory requirements. All CRF entries will be verified with source documentation. The review of medical records will be done in a manner to assure that patient confidentiality is maintained.

10.2 Curricula Vitae and Financial Disclosure of Investigators

All Principal Investigators will be required to provide a current signed and dated curriculum vitae, a completed FDA Form 1572 (required in the USA) and a financial disclosure statement (required in the USA) to Theradex®. All Sub-investigators will be required to provide a current curriculum vitae and a financial disclosure statement (required in the USA) to Theradex®.

10.3 Protocol Modifications

No modification of the protocol should be implemented without the prior written approval of the Sponsor or the Sponsor's representative (Theradex®). Any such changes which may affect a patient's treatment or informed consent, especially those increasing potential risks, must receive prior approval by the IRB/IEC. The exception to this is where modifications are necessary to eliminate an immediate hazard to trial subjects, or when the change involves only logistical or administrative aspects of the trial (e.g., change in monitor, change in telephone number). Other administrative revisions which may impact the clinical portion of a study will be duly reported to the IRB/IEC by the Principal Investigator.

10.4 Publication Policy

The Investigator agrees to inform the Sponsor of any publication or presentations on the study. All manuscripts, abstracts or presentations (in outline form with copies of slides if available) will

be submitted to the Sponsor and Theradex® at least 30 days prior to the submission of the data for publication in order for the Sponsor to protect proprietary information. The Sponsor will review the submitted material within a reasonable period of time and will not unreasonably withhold publication permission.

11.0 ETHICAL CONSIDERATIONS

11.1 Informed Consent

The Investigator will obtain written informed consent from each patient, or their authorized representative, participating in the study. The form must be signed, witnessed and dated. The informed consent form will contain all the Essential Elements of Informed Consent set forth in 21 CFR, Part 50, the European Union Directive 2001/20/EC and its associated Detailed Guidances, European Union GCP Directive 2005/28/EC, the ICH Guideline for Good Clinical Practice, Section 4.8, and the terms of the Declaration of Helsinki (2013). Copies of the signed document should be given to the patient and filed in the Investigator's study file, as well as the patient's medical record if in conformance with the institution's Standard Operating Procedures.

In cases where minors or incapacitated subjects are to be included, two sets of information sheets might be needed according to national regulations. In addition to the information given to the patient's parent or legal representative, the patient should be given information according to his/her capacity to understand. This information should include, where appropriate, a statement that the patient's decision not to participate or to withdraw from a trial will be respected, even if consent is given by the parent/legal representative.

11.2 Institutional Review Board/Independent Ethics Committee

The study will not be initiated without approval of the appropriate Institutional Review Board/Independent Ethics Committee (IRB/IEC) and compliance with all administrative requirements of the governing body of the institution. This protocol, consent procedures, and any amendments must be approved by the IRB/IEC in compliance with current regulations of the FDA and the European Union as applicable and in accordance with ICH/GCPs. A letter of approval will be sent to the Sponsor prior to initiation of the study and when any subsequent modifications are made. The IRB/IEC will be kept informed by the Investigator, Theradex® or the Sponsor, as required by national regulations, as to the progress of the study as well as to any serious and unexpected adverse events.

11.3 Patient Privacy

In order to maintain patient confidentiality, all case report forms, study reports and communications relating to the study will identify patients by initials and assigned patient

numbers; patients should not be identified by name. In accordance with local, national or federal regulations, the Investigator will allow the Sponsor or designee personnel access to all pertinent medical records in order to verify the data gathered on the case report forms and to audit the data collection process. Regulatory agencies such as the US Food and Drug Administration (FDA) and the UK Medicine and Healthcare Products Regulatory Agency (MHRA) may also request access to all study records, including source documentation for inspection. Clinical information will not be released without the written permission of the patient as outlined in the patient consent form.

12.0 DATA HANDLING AND RECORD KEEPING

12.1 Data to be Recorded Directly in the Electronic Case Report Form

Not applicable.

12.2 Recording of Data

Data collected during the study will be recorded in the patient's eCRFs by the investigational site staff. The staff will keep records of the patient's visit in the files considered as source documents for the site, e.g., hospital chart, research chart. The Investigator will be responsible for the recording of all data on the CRF and for submitting the data to the Sponsor or their designee in a timely manner. Should any value be significantly different from normal, the Investigator will comment in the appropriate sections provided in the CRF.

12.3 Study Records

U.S. Federal laws require that an Investigator maintain all study records for the indication under investigation for two years following the date a Product Licensing Application is approved or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and the FDA is notified.

European laws require that the Investigator maintain all study records (excluding the subject's medical files, see below):
- for at least 15 years after completion or discontinuation of the trial,
- or for at least two years after the granting of the last marketing authorization in the European Community (EC) and where there are no pending or contemplated marketing applications in the EC,
- or for at least two years after the formal discontinuation of clinical development of the investigational product.

Subject's medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

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APPENDIX I - ECOG PERFORMANCE STATUS

Grade	
0	Fully active, able to carry on all pre-disease performance without restriction.
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.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.