Development of an alkalizing antibody-enzyme conjugate for NSCLC treatment that is in Phase I clinical testing

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Abstract

L-DOS47 is an antibody-enzyme conjugate developed to treat non-small cell lung cancer. L-DOS47 has been studied in a full range of preclinical studies including tissue screening, cytokine release and animal toxicological studies. In the primate GLP study, L-DOS47 (0, 17, 26, and 35 µg/kg) was administered by IV infusion on Days 1, 8, 15 and 22, followed by a 28-day recovery period. No treatment related clinical signs were observed for the animals treated with 17 or 26µg/kg of L-DOS47. Adverse signs were observed in some but not all of the high dose (35 µg/kg) treated animals. Based on adverse clinical signs observed at 35µg/kg, the NOAEL was determined to be 26 µg/kg/day in this study. Currently L-DOS47 is approved for phase I/II studies in Europe and the U.S.A. Patient enrollment has begun in Poland.

Background

Many solid human tumors generate an acidic and hypoxic microenvironment as a result of altered metabolic pathways and aberrant tumor vasculature. In certain tumors, the chronic exposure to acidic extracellular conditions has been reported to promote invasiveness and metastatic behaviour. In addition, the lower pH may promote resistance to weakly basic chemotherapeutic agents by altering their partitioning coefficient between the extracellular and intracellular compartments. L-DOS47 has been developed to target this unique tumor microenvironment. L-DOS47 is a conjugate of a lung adenocarcinoma specific single domain antibody and a urease enzyme. The antibody serves as a targeting agent to deliver the enzyme to the affected site while the urease enzyme coverts urea, an abundant metabolite, into ammonia and generates a local pH increase.

Preclinical Studies

Summary of Pivotal GLP Primate Study

Species	Duration of Dosing	Doses (µg/kg)
Cynomolgus Monkey	1-month (Days 1, 8, 15 and 22)	0, 17, 26, 35

Dose (µg/kg)	Note-worthy findings
0	none
17	No-treatment related clinical signs
26	No-treatment related clinical signs
35	Some animals experienced decreased activities, tremors, labored breathing; foamy vomitus found in some cages. One animal euthanized moribund, others recovered

Dose (µg/kg)	Serum Chemistry including Cytokine release
0	unremarkable
17	unremarkable
26	IL6 increase
35	IL6 and APL (females) increase

Doses (µg/kg)	Immunogenicity
0	none
17	5 out of 20 (1M 4F)
26	16 out of 30 (8M, 8F)
35	21 out of 36 (11M, 10F)

Starting Dose Derivations

Starting clinical dose was derived after comparing NOAEL, MABEL and TK information from both rat and monkey studies

NOAEL

Species	NOAEL	HED	Starting Dose*
Monkey	26 µg/kg	8.7 µg/kg	0.19 µg/kg
Rat	85 µg/kg	12 µg/kg	0.27 µg/kg

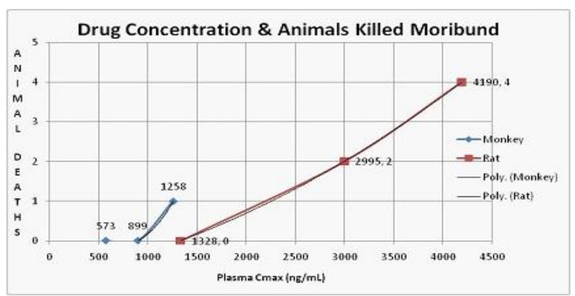
**1/10 of HED / 4.5 (antigen affinity)*

MABEL

Studies	Effectiv HED	Starting Dose
A549 cell	32 µg/kg	3.2 µg/kg
A549 xeno.	1.55 µg/kg	0.155 µg/kg

TK (monkey data shown only)

Dose (µg/kg)	Cmax (ng/mL)	Starting Dose
17	573 / 500	0.17 / 0.13
26	899	0.26
35	1258	n/a



Clinical Study

Starting Dose Selection

Method	Possible Starting Dose µg/kg
NOAEL	0.19 (monkey)
MABEL	0.155
TK (Cmax)	**0.13** (accepted)

A Phase I/II open-label, non-randomized dose escalation study in non-squamous non-small cell lung cancer patients (active site: Poland)

Primary obj. (I): To define the MTD of multiple doses of L-DOS47

Primary obj. (II): To make a preliminary assessment of the efficacy of L-DOS47

Secondary obj. (I&II): To evaluate pharmacokinetics, immunogenicity, safety and tolerability

Cohort	Doses (µg/kg)	Treatment
8 (3 pt. each)	0.13, 0.21, 0.33, 0.40, 0.59, 0.78, 1.04, 1.38	One cycle= 2 weekly i.v. infusion with one week rest. 4 cycles max

Two cohorts completed with no treatment related SAE

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