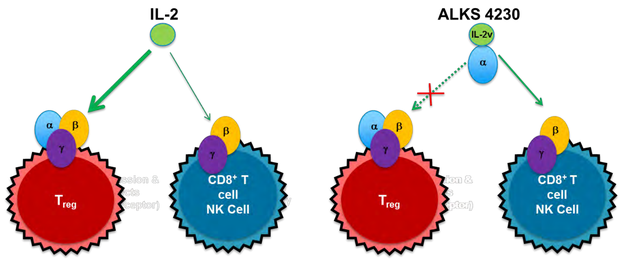
Pharmacokinetics and Pharmacodynamic Effects of ALKS 4230, an Investigational Immunotherapeutic Agent, in Cynomolgus Monkeys After Intravenous and Subcutaneous Administration

Lei Sun, Jared E. Lopes, Heather L. Flick, Erin A. Murphy, Heather C. Losey
Alkermes, Inc., Waltham, MA, USA

BACKGROUND

- ALKS 4230 is an engineered cytokine designed to selectively activate the intermediate-affinity interleukin-2 receptor (IL-2R), expressed predominantly on natural killer (NK) cells and memory subsets of CD8⁺ T cells and CD4⁺ T cells, which are known to play an important role in driving immune responses to various types of cancer.
- In contrast, wild-type IL-2 preferentially activates the high-affinity IL-2R, driving the activation and expansion of immunosuppressive CD4⁺ regulatory T cells (T_{regs}), which are thought to limit anticancer activity in response to treatment with high dose recombinant human IL-2 (rhIL-2, i.e. aldesleukin).[1]



- *In vitro* and *in vivo*, ALKS 4230 selectively activates and expands NK cells and memory phenotype CD8⁺ T cells, with reduced activation and expansion of T_{regs} compared to rhIL-2.
- *In vitro* potency of ALKS 4230 on activating lymphocyte populations was similar between human and cynomolgus monkey, suggesting cynomolgus monkey is a pharmacologically relevant species for predicting immunologic activity in human.

In Vitro Potency	NK Cells	CD8⁺ T Cells	T_{regs}
EC_{10} (nM)			
Human	0.09 ± 0.08	0.18 ± 0.06	0.13 ± 0.09
Monkey	0.10 ± 0.03	0.32 ± .012	0.11 ± 0.03
EC_{50} (nM)			
Human	0.46 ± 0.08	1.1 ± 0.1	0.59 ± 0.24
Monkey	0.48 ± 0.22	1.3 ± 0.4	0.50 ± 0.14

Data presented are mean ± standard deviation values generated from three experiments with each sample being stimulated in triplicate.

- A first-in-human study of intravenous (IV) administration of ALKS 4230 in patients with advanced solid tumors (NCT02799095) is currently ongoing.
- To compare the pharmacodynamic effects of ALKS 4230 after IV and subcutaneous (SC) administration, two studies were carried out in cynomolgus monkeys.

METHODS

Experimental Design

- Study 1: A single dose of ALKS 4230 was administered intravenously at 0.3 mg/kg or subcutaneously at 0.3 mg/kg or 1 mg/kg to 3 groups of male drug-naïve cynomolgus monkeys (3/dose group).
- Study 2: ALKS 4230 was administered intravenously at 0.1 mg/kg/dose once daily for 5 days (Days 1-5) or subcutaneously at 0.5 mg/kg/dose on Day 1 and Day 4 to 2 groups of male drug-naïve cynomolgus monkeys (n=3/group).
- Serial blood samples were collected from each animal for determination of serum concentrations of ALKS 4230 as well as for immunophenotyping by flow cytometry.

Pharmacokinetic Evaluation

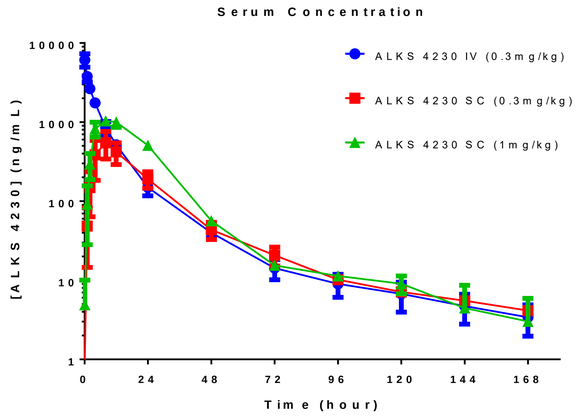
- Serum concentrations of ALKS 4230 were determining using an electrochemiluminescense method.
- PK parameters were calculated by non-compartmental analysis.

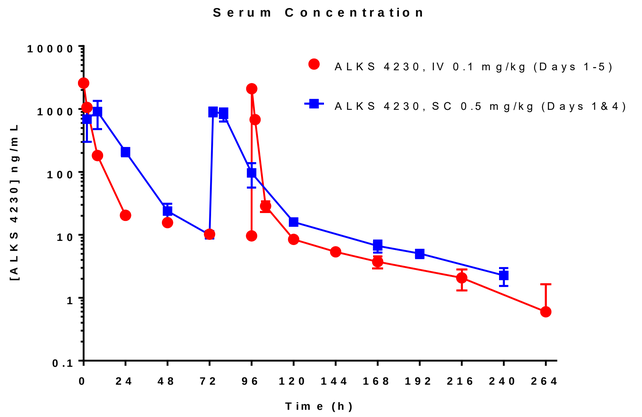
Pharmacodynamic Analysis

- Peripheral whole blood was collected prior to and at 3, 6-10, 14, and 21 days post the first dose administration on Day 1.
- Red blood cells were lysed, remaining cells were stained with different panels of antibodies to identify various immune populations, fixed/permeabilized, and stained intracellularly for FoxP3.

RESULTS

ALKS 4230 Pharmacokinetics After Single- and Multiple-Dose IV or SC Administration

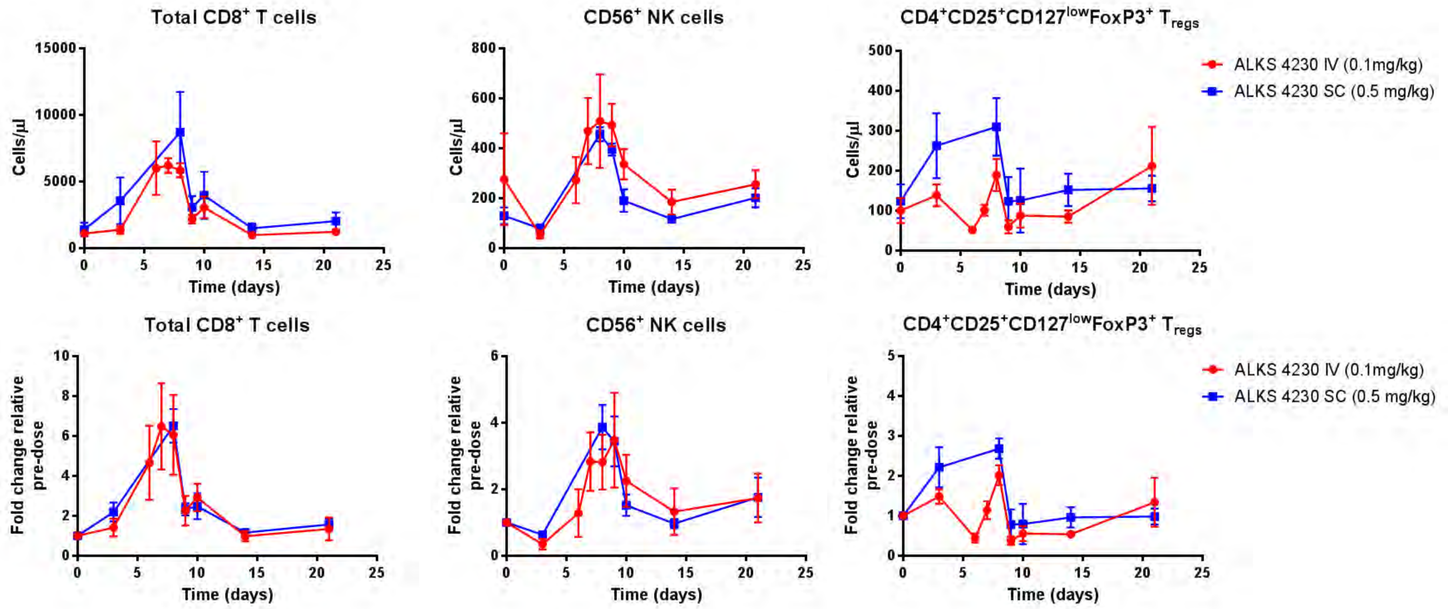




- After a single SC dose of ALKS 4230, t_{max} was observed at 8 hours.
- Peak (C_{max}) and total (AUC_{∞}) systemic exposure of ALKS 4230 increased with increases in dose.
- Bioavailability after SC administration was estimated to be 45% at 0.3 mg/kg and 28% at 1 mg/kg.
- AUC_{∞} was similar, C_{max} was ~6-fold lower after a single SC dose of 1 mg/kg compared to after an IV dose of 0.3 mg/kg.

- C_{max} after SC doses of 0.5 mg/kg was 2- to 3-fold lower than that after IV doses of 0.1 mg/kg.
- Trough serum concentrations on Day 4 (72 hours post the 1st first) were similar between the two dosing regimens.
- Total systemic exposures (AUC_{total}) of ALKS 4230 after 5 daily IV doses of 0.1 mg/kg and 2 SC doses of 0.5 mg/kg (on Days 1 and 4) were similar.

Pharmacodynamic Response After Multiple-Dose IV (Days 1-5) or SC (Days 1&4) Administration of ALKS 4230



- IV and SC administration of ALKS 4230 resulted in notable increases in CD8⁺ T cells and CD56⁺ NK cells but only a small increase in CD4⁺ T_{regs}
- IV and SC administration of ALKS 4230 induced a similar ~ 6-fold increase in CD8⁺ T cells and an ~ 4-fold increase in CD56⁺ NK cells at day 8.

- ALKS 4230 induced changes in CD8⁺ T cells and CD56⁺ NK cells were transient, with cell numbers returning to predose levels by day 21.
- A number of blood samples harvested at days 6 and 7 from the SC group were received frozen and therefore were excluded from the analyses.

CONCLUSIONS

- SC administration of ALKS 4230 can achieve similar total systemic exposure compared to IV administration with less frequent dosing and a lower C_{max}, resulting in similar expansion of CD8⁺ T cells and CD56⁺ NK cells
- These data support further clinical evaluation of SC administration of ALKS 4230 as a practical alternative to IV dosing

REFERENCES

1. Sim GC et al. IL-2 therapy promotes suppressive ICOS⁺ T_{reg} expansion in melanoma patients. *J Clin Invest* 2014;124:99-110.

DISCLOSURES

This study was funded by Alkermes, Inc. All authors are employees of Alkermes, Inc.

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