380 GS-3583, A NOVEL FLT3 AGONIST FC FUSION PROTEIN, EXPANDS CONVENTIONAL DENDRITIC CELLS IN HEALTHY VOLUNTEERS

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Background Conventional dendritic cells subtype 1 (cDC1) play a vital role in the priming and expansion of tumor specific CD8+ T cells and their recruitment to tumor microenvironment (TME). However, cDC1s are often underrepresented in the TME. Systemic administration of Fms-like tyrosine kinase 3 ligand (FLT3L), a hematopoietic growth factor that binds to FLT3 on myeloid and lymphoid progenitor cells, leads to expansion of cDC1s in the periphery which can then be recruited into the TME. FLT3 pathway stimulation using GS-3583, a novel FLT3 agonistic Fc fusion protein, has the potential to promote T cell mediated anti-tumor activity. We sought to evaluate the pharmacodynamic (PD) effect of a single dose of GS-3583 in healthy volunteers alongside its safety. Herein, we present the updated results of the study.

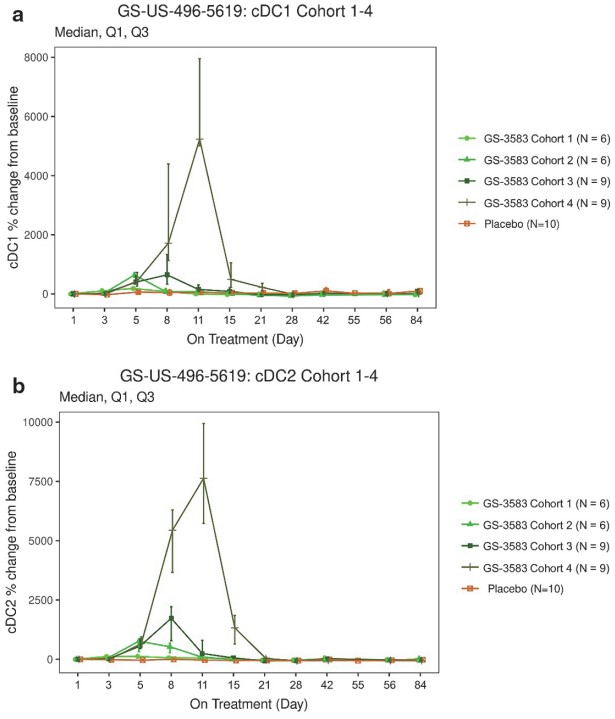
Methods This was a first-in-human, placebo-controlled study of GS-3583 in healthy volunteers to evaluate the safety, pharmacokinetics (PK), and PD of escalating single doses (ranging from 75 micrograms to 2000 micrograms) of GS-3583. The study was blinded to the subjects and the investigator. Each dose cohort enrolled 8–12 healthy subjects who received GS-3583 or placebo as single IV infusion at 3:1 ratio. Subjects were observed in the phase 1 unit for 15 days and then for 12 weeks as outpatients. As part of the PD evaluation, we investigated the changes in the number of cDC1 and cDC2 cells.

Results As of 2nd July 2021, selected safety, PK and PD data from all 4 cohorts were available. GS-3583 was well tolerated and all subjects had been discharged. To date, there have been no serious or grade 3 or higher adverse events. Preliminary PK analysis suggested dose-dependent increase in GS-3583 exposure (AUC and Cmax). Preliminary PD analysis shows that administration of GS-3583 resulted in temporary, dose-dependent increases in cDC1/cDC2 cells that peaked between days 5–11 (higher doses resulted in later peaks) and returned to baseline within 3 weeks of drug administration (table 1, figure 1).

Abstract 380 Table 1 Selected subject characteristics and pharmacodynamic results

Cohort	1	2	3	4
Subjects treated (A=active; P=placebo)	8 (6A; 2P)	8 (6A; 2P)	12 (9A; 3P)	12 (9A; 3P)
Age, years median (range)	32 (20, 38)	27 (23, 45)	22 (18, 45)	31.5 (18, 42)
Male n (%)	5 (62.5%)	5 (62.5%)	8 (66.7%)	9 (75.0%)
cDC1 peak cell count* median (Q1, Q3)	**Day 5** 69.6 (62.9, 89.2)	**Day 5** 169.0 (121.1, 215.1)	**Day 8** 147.2 (130.1, 258.6)	**Day 11** 922.2 (528.6, 1355.2)
cDC1, fold change from baseline* median (Q1, Q3)	**Day 5** 1.85 (1.38, 2.4)	**Day 5** 6.42 (5.62, 7.17)	**Day 8** 6.47 (3.29, 13.31)	**Day 11** 52.33 (50.01, 79.53)
cDC2 peak cell count* median (Q1, Q3)	**Day 5** 1346.0 (1124.8, 1395.1)	**Day 5** 2937.0 (1679.8, 3731.9)	**Day 8** 10677.6 (7565.6, 13702.6)	**Day 11** 36741.8 (29835.8, 55246.2)
cDC2, fold change from baseline* median (Q1, Q3)	**Day 5** 1.20 (0.71, 1.85)	**Day 5** 7.61 (3.21, 8.03)	**Day 8** 17.30 (7.86, 22.13)	**Day 11** 76.33 (57.33, 99.42)

* Data shown only from the subjects who received GS-3583; placebo data are excluded



Abstract 380 Figure 1 A) Comparison of cDC1 cell quantitative changes in cohorts 1–4; B) Comparison of cDC2 cell quantitative changes in cohorts 1–4

Conclusions GS-3583 infusion was well tolerated and induced dose dependent expansion of dendritic cells in the periphery in healthy volunteers. In patients with cancer, this increase in dendritic cells can be utilized to enhance anti-tumor therapeutic effects of immuno-oncology therapies.

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Ethics Approval The study received study site IRB/Ethics Committee approval prior to enrollment of subjects.

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