ABSTRACT NUMBER: 2518

GS-9876, a Novel, Highly Selective, SYK Inhibitor in Patients with Active Rheumatoid Arthritis: Safety, Tolerability and Efficacy Results of a Phase 2 Study

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SESSION INFORMATION

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Session Type: ACR Poster Session C

Session Title: Rheumatoid Arthritis – Treatments Poster III: Biosimilars and New Compounds

Session Time: 9:00AM-11:00AM

Background/Purpose:

Spleen tyrosine kinase (SYK) mediates immunoreceptor signaling and is essential in activation of cells including B lymphocytes, monocytes, macrophages, dendritic cells, and osteoclasts. SYK may play an important role in the initiation and progression of autoimmune diseases, including rheumatoid arthritis (RA) and lupus. GS-9876 is a novel, potent, highly selective, oral inhibitor of SYK in phase 2 trials for autoimmune diseases.

Methods:

Patients with active RA with prior inadequate response to methotrexate (MTX) or a biologic anti-rheumatic drug were randomized 1:1:1:1 to receive GS-9876 30 mg, GS-9876 10 mg, selective JAK inhibitor filgotinib (FIL) 200 mg or matching placebo once daily for 12 weeks on a stable background of oral MTX. The primary endpoint for GS-9876 was the change in DAS28(CRP) at week 12. Pharmacokinetics (PK) and various biomarkers were evaluated at several time points, including VectraDA and stimulation of whole blood in TruCulture (MyriadRBM) tubes.

Results:

A total of 83 patients received study drug and 79 completed the study. Fourteen patients (16.9%) were male and 69 (83.1%) were female. The majority were white (77 patients, 92.8%). The mean (SD) age at baseline was 55 (11.5) years (range 18 to 73). The primary and secondary endpoints are reported in Table 1. For DAS28(CRP), the mean (SD) at baseline was 5.75 (0.961) with a median of 5.69; a statistically significant reduction at week 12 was observed only in patients receiving FIL as compared to placebo (Table 1). Adverse events (AE) were reported across all groups (37.5% in the combined GS-9876 arms, 38.1% in FIL, 40.9% in placebo). No deaths or serious AE were reported.

Plasma exposures of all study drugs were comparable to those observed in healthy subjects and historical data. *Ex vivo* stimulated whole blood identified differential responses between GS-9876 and placebo.

Conclusion:

Clinical efficacy of GS-9876 in RA was not observed, but GS-9876 was safe and well-tolerated over a 12 week period in patients with active RA on MTX. FIL showed favorable safety and clinical efficacy consistent with prior data, validating the study concept and design. Additionally, biomarker changes with GS-9876 support the continuation of studies in lupus-related diseases.

Table 1. Key endpoints at week 12; *p(compared to placebo)

	DAS28(CRP) **Primary endpoint** **(mean change from baseline to week 12)**	**ACR20/50/70** **Secondary endpoints** **(% achieving at week 12)**	**HAQ-DI** **Secondary endpoint** **(mean change from baseline to week 12)**
Placebo	-1.36 (1.044)	40.9 / 22.7 / 13.6	-0.39 (0.389)
GS-9876 10 mg	−0.78 (1.119)	25.0 / 20.0 / 15.0	-0.18 (0.800)
GS-9876 30 mg	−1.26 (1.276)	35.0 / 20.0 / 5.0	-0.46 (0.480)
Filgotinib 200 mg	−2.46 (1.242); *p=0.002	81.0 / 47.6 / 38.1	-0.70 (0.649)

Disclosure: A. J. Kivitz, Novartis, 1,AbbVie, Janssen, Pfizer, UCB, Genzyme, Sanofi, Regeneron, Boehringer-Ingelheim, Sun Pharma, 5,Celgene, Novartis, Genentech, Merck, Horizon, Flexion, Ironwood, Regeneron, Sanofi, Pfizer, 8; **D. P. Mehta**, None; **F. Matzkies**, Gilead Sciences, Inc., 1, 3; **A. Mozaffarian**, Gilead Sciences, Inc., 1, 3; **R. Kunder**, Gilead Science, Inc, 1, 3; **J. Di Paolo**, Gilead Sciences, 1, 3; **N. Mozaffarian**, Gilead Science Inc, 1, 3; **S. Hsueh**, Gilead Sciences, Inc., 1, 3; **J. Kim**, Gilead Sciences, Inc., 1, 3; **W. Jiang**, Gilead Sciences, Inc., 1, 3; **L. Liu**, Gilead Sciences, Inc., 1, 3; **J. S. Sundy**, Gilead Sciences, Inc., 1, 3; **M. C. Genovese**, Gilead, Galapagos, Abbvie, Lilly, Pfizer, 2,Gilead, Galapagos, Abbvie, Lilly, Pfizer, 5.

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