in UST-NR or PBO patients. IGS levels were elevated in 67% of patients at baseline versus healthy controls. Serum INF-γ levels and IGS levels in blood were not modulated by UST treatment through week 24. Baseline IFN-I signature status did not associate with response to UST, as the treatment effect size (UST vs PBO) was similar in IGS low (A=27%) and high (A=28%) patients.

**Conclusion:** Response to UST was associated with reductions in INF-γ levels, whereas IL-17A, IL-17F, IL-22 and IFN-γ remained largely unchanged. While these findings require confirmation in an ongoing Phase 3 study, these data implicate the involvement of the IL-12 pathway and suggest a novel mechanism of action for UST-R in SLE.

**REFERENCES:**


**Background:** Systemic lupus erythematosus (SLE) is an autoimmune disease that can affect multiple organs, including the skin, joints, and kidneys. The disease is characterized by the development of skin lesions, autoantibody production and inflammation-induced glomerulonephritis. The skin is involved in up to 85% of SLE cases. In the MRL/lpr spontaneous mouse model of SLE, disease symptoms also include lymphocyte hyper-proliferation, resulting in lymphadenopathy and splenomegaly. The evolutionary conserved Janus kinase-signal transducer of activators of transcription (JAK-STAT) pathway constitutes a rapid membrane to nucleus signaling modality that affects key biological aspects of the mammalian immune system. Janus kinase 1 (JAK1) is involved in the downstream signaling pathway of type I interferons (IFNs), and high levels of type I IFNs are associated with SLE. JAK1 is an oral small molecule JAK1 selective inhibitor currently in development.

**Objectives:** To determine the effectiveness of INCB054707, a selective JAK1 inhibitor, in a preclinical model of cutaneous lupus erythematosus.

**Methods:** Female MRL/lpr mice were randomized to treatment groups at 11 weeks old to receive twice daily oral doses of vehicle (0.5% methyl cellulose) or INCB054707 at 10, 30, or 90 mg/kg for 10 weeks. Efficacy was determined by weekly scoring of the changes in skin, lymph node size, and proteinuria. At study termination (week 21), inguinal lymph nodes and spleens were excised and weighed, skin lesions and kidneys were excised and fixed for histopathologic analysis, and serum was collected for pharmacokinetic analysis and ELISA. Autoantibody presence in the serum was detected using a commercial anti-dsDNA ELISA kit.

**Results:** In vitro enzymatic selectivity screening of INCB054707 revealed JAK1 IC50 = 8.9 nM versus JAK2 IC50 = 463 nM, resulting in a JAK1/JAK2 selectivity ratio of 51.

**References:**


**Disclosure of Interests:** Matteo Cesaroni None declared, William Murray Brown None declared, Cristina Croia None declared, Davide Lucchesi None declared, Felice Rivellesi None declared, Liliane Fossati-Jimack None declared, Edoardo Prediletto None declared, Elisa Corsiero None declared, Francesca Barone Grant/research support from: GlaxoSmithKline, Pfizer, ROCHE, and UCB, Consultant for: AbbVie, AstraZeneca, Biotech, Bristol-Myers Squibb, Celgene, Crescendo, GSK, and Vertex. Speakers bureau: AbbVie, AstraZeneca, Biotech, Bristol-Myers Squibb, Celgene, Crescendo, GlaxoSmithKline, Janssen, Lilly, Merck, Novartis, Pfizer, ROCHE, UCB, and Vertex.

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