Abstract Number 142
A PHASE IIA STUDY OF NOVEL MATURATION INHIBITOR GSK2838232 IN HIV PATIENTS
Edwin DeJesus1, Sara Harward2, Roxanne C. Jewell2, Mark Johnson2, Etienne Dumont3, Viviana Wilches3, Fiona Halliday4, Christine Talarico2, Jerry Jeffrey2, Kevin Gan3, Franco B. Felizarta5, Anita Scribner6, Moti Ramgopal7, Paul Benson8, Brian A. Johns2
1Orlando Immunology Center, Orlando, FL, USA, 2GlaxoSmithKline, Research Triangle Park, NC, USA, 3GlaxoSmithKline, Collegeville, PA, USA, 4GlaxoSmithKline, Uxbridge, UK, 5Private Practice, Bakersfield, CA, USA, 6DCOL Center for Clinical Research, Longview, TX, USA, 7Midway Immunology and Research Center, Fort Pierce, FL, USA, 8Be Well Medical Center, Berkley, MI, USA

Background:
GSK2838232 is a second-generation HIV maturation inhibitor with a distinct preclinical virologic profile and well-defined pharmacokinetics (PK), safety, and tolerability in non-HIV-infected subjects that suggests potential to overcome hurdles met by prior drugs in this class. This profile provided rationale for investigation of GSK2838232 co-administered with cobicistat in HIV-1-infected adults.

Methods:
This proof of concept Phase IIa study assessed GSK2838232 antiviral activity, PK, safety, and tolerability in HIV infected adults currently off antiretroviral therapy. The dose-ranging two-part study evaluated 4 dose levels of once daily GSK2838232 monotherapy administered with 150 mg cobicistat for 10 days. PK samples were collected at Days 1 and 10, and safety assessments were performed throughout the study. Subjects were followed for 11 days after the end of treatment (Day 21).

Results:
A total of 33 subjects were enrolled across 4 cohorts (200 mg n=8, 100 mg n=10, 50 mg n=8 and 20 mg n=7) of GSK2838232. Following completion of the 100 mg cohort, an interim safety and PK analysis was performed, then remaining cohorts enrolled. Dose-proportional increases in drug exposure were seen. There was moderate-to-high PK variability, with steady state by Day 8 and a geometric mean plasma t½ on Day 10 of 16-19 h across the dose levels. GSK2838232 monotherapy showed a reduction in plasma HIV-1 RNA from baseline to Day 11, with a mean maximum decrease of 1.70, 1.32, 1.56 and 0.67 log10 copies/mL at the 200, 100, 50 and 20 mg dose levels respectively. The population viral genotype was assessed pre- and post-GSK2838232 dosing. Of the 28 subjects with reported genotype data, 2 subjects had treatment-emergent A364A/V mixtures associated with in vitro GSK2838232 resistance. Of these 2 subjects, 1 subject had phenotypic resistance to GSK2838232. Study drug was well-tolerated with no clinically relevant trends in laboratory values, vital signs, or cardiac signals. There were no serious adverse events and all adverse events (AEs) were mild to moderate. There were 5 subjects assessed as experiencing 6 possible drug-related AEs: headache (n=2), somnolence (n=1), skin rash (n=1), abnormal dream (n=1) and pruritus (n=1).

Conclusion:
GSK2838232 demonstrated short-term tolerability and antiviral activity, with the maximal response observed in the highest dose cohort. Preliminary evidence of clinical activity observed in HIV patients provides a positive proof of concept for further exploration of GSK2838232.