Potent Antiviral Activity of S/GSK1349572, A Next Generation Integrase Inhibitor (INI), in INI-Naïve HIV-1-Infected Patients: ING111521 Protocol

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Integrase Inhibitors: Future Cornerstones of HIV Therapy

- **INIs have been demonstrated to be amongst most potent ARVs on market**
  - **In studies of treatment-experienced patients, 50% of subjects with no active drugs in background regimen (PSS=0) achieved undetectable HIV RNA[1]**
- **INI are amongst best tolerated ARVs on market**
  - **In studies of treatment-experienced patients, AE rates were comparable to placebo[1]**
  - **In studies of treatment-naïve patients, the proportion of subjects reporting AEs were lower than with EFV[2]**

1. Steigbigel RT. *NEJM* 2008; 359:339-54.
2. Lennox J. ICAAC/IDSA 2008, Wash DC, Abstract H-896a.

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Concept of Next Generation HIV Integrase Inhibitor

- HIV PIs have evolved over time to deliver better convenience, tolerability, and barrier to resistance
  - INI class is poised to evolve similarly
- Next Generation INIs should provide real advances for patients, including:
  - QD dosing potential
  - Unique resistance profile

S/GSK1349572 engineered to deliver these attributes

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S/GSK1349572 Key Characteristics

- **Pharmacokinetics**
  - **Once daily dosing ($t_{1/2}$ =15 hrs), low milligram dose[1]**
  - **Low PK variability[1,2]**
  - **Predictable exposure-response relationship[2]**
  - **No significant food effect[1]**
  - **No CYP induction or inhibition[1]**
- **Unique resistance profile**
  - **Limited cross-resistance to raltegravir and elvitegravir[3,4]**
  - **Potential for higher genetic barrier to resistance[3]**

[1] Min S, et al. IAS 2009, Cape Town, Wednesday poster #WEPEA099.
[2] Song I, et al. IAS 2009, Cape Town, Wednesday poster #WEPEB250.
[3] Sato A, et al. IAS 2009, Cape Town, Wednesday poster #WEPEA097.
[4] Underwood M, et al. IAS 2009, Cape Town, Wednesday poster #WEPEA098.

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ING111521 Phase IIa Study Design

- Randomized, placebo-controlled, double-blind, parallel group, 10-day monotherapy
- 3 cohorts of 10 subjects (8 active, 2 PBO) planned
  - S/GSK1349572 doses: 2 mg, 10 mg, 50 mg
  - Subjects blinded within cohort to active v. PBO
- Key Inclusion and Exclusion
  - INI-naïve, treatment-naïve or experienced
  - CD4 cell count ≥ 100 cells/mm^3
  - HIV-1 RNA ≥ 5000 cp/mL
  - No HIV treatment for 12 weeks
- Primary Endpoint: change from baseline in HIV RNA

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Baseline Characteristics

Baseline Characteristic	S/GSK1349572 Once Daily Dose 2mg N=9	10mg N=9	50mg N=10	Placebo N=7
Gender[1]	100%M	100%M	100%M	100%M
Race[1]	7W:2AA	9W	7W:3AA	5W:2AA
Age (Mean)	41	40	34	40
Plasma HIV-1 RNA log_{10} copies/mL median (min, max)	4.40 (4.03, 4.85)	4.48 (4.25, 5.54)	4.51 (3.85, 5.17)	4.11 (4.03, 4.74)
CD4+ cell count cells/mm^3 median (min, max)	435 (175, 797)	398 (171, 509)	502 (232, 577)	427 (123, 1222)

1. M = Male; W = White/Caucasian; AA = African-American

35 US subjects enrolled and completed all visits.

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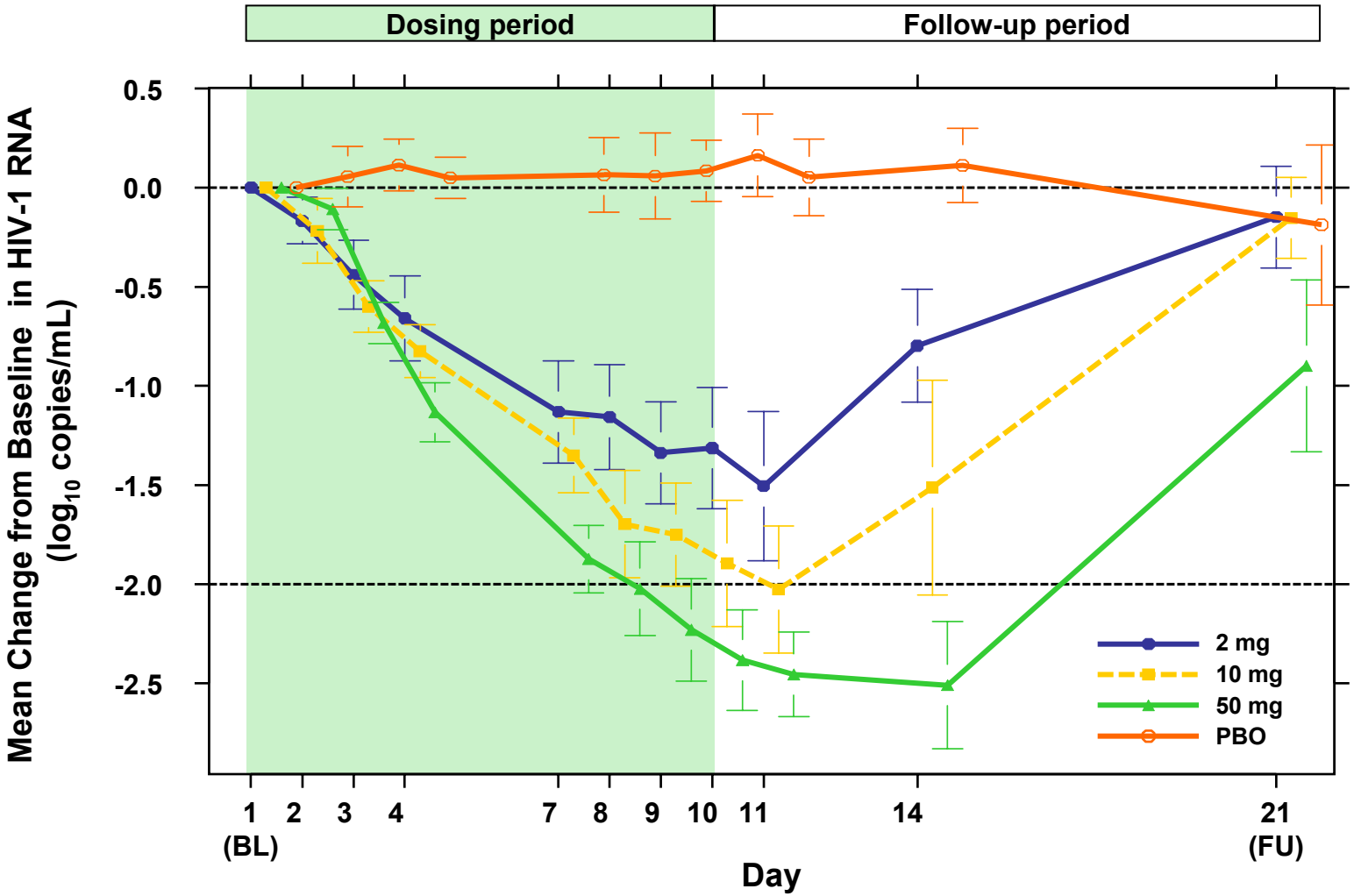
S/GSK1349572: Unprecedented Antiviral Activity



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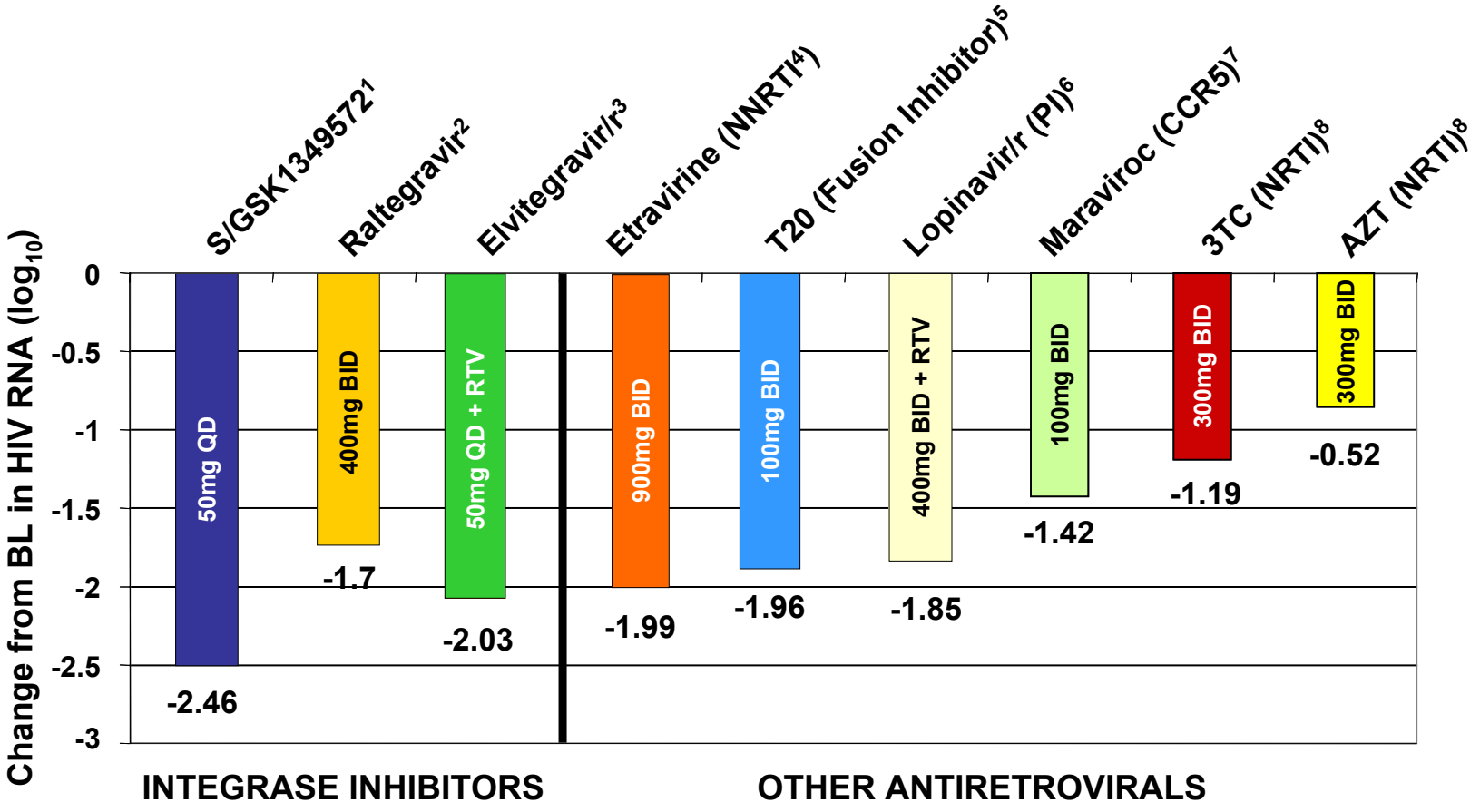
S/GSK1349572 Monotherapy



1. Lalezari J. 5th *IAS 2009*, *Cape Town,* abstract TUAB105.
2. DeJesus E. *J Acquir Immune Defic Syndr* 2006 ; 43:1-5.
3. Markowitz et al. *JAIDS* Volume 43(5) 15 December 2006 pp 509-515.
4. Sankatsing et al. *AIDS* 2003, 17:2623–2627.
5. Kilby JM. AIDS Res Hum Retroviruses 2002; 18:685-694.
6. Murphy RL. *AIDS* 2001;15:F1-F9.
7. Fätkenheuer G et al. *Nat Med* 2005 Nov; 11:1170-1172.
8. Eron JJ, *N Engl J Med* 1995, 333:1662-1669.

Proportion of Subjects With Undetectable HIV RNA at Nadir

	S/GSK1349572 Dose		
HIV RNA	2mg (n=9)	10mg (n=9)	50mg (n=10)
<400 copies/mL	5/9 (56%)	5/9 (56%)	9/10 (90%)
<50 copies/mL	1/9 (11%)	0	7/10 (70%)

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Median CD4 Change to Day 11

	S/GSK1349572 Dose			
	2mg	10mg	50mg	Placebo
Baseline CD4 (cells/mm^3) (min, max)	435 (175, 797)	398 (171, 509)	502 (232, 577)	427 (123, 1222)
Day 11 Change from Baseline (cells/mm^3) (min, max)	15 (-286, 222)	106 (-39, 142)	64 (-155, 523)	-28.5 (-247, 50)

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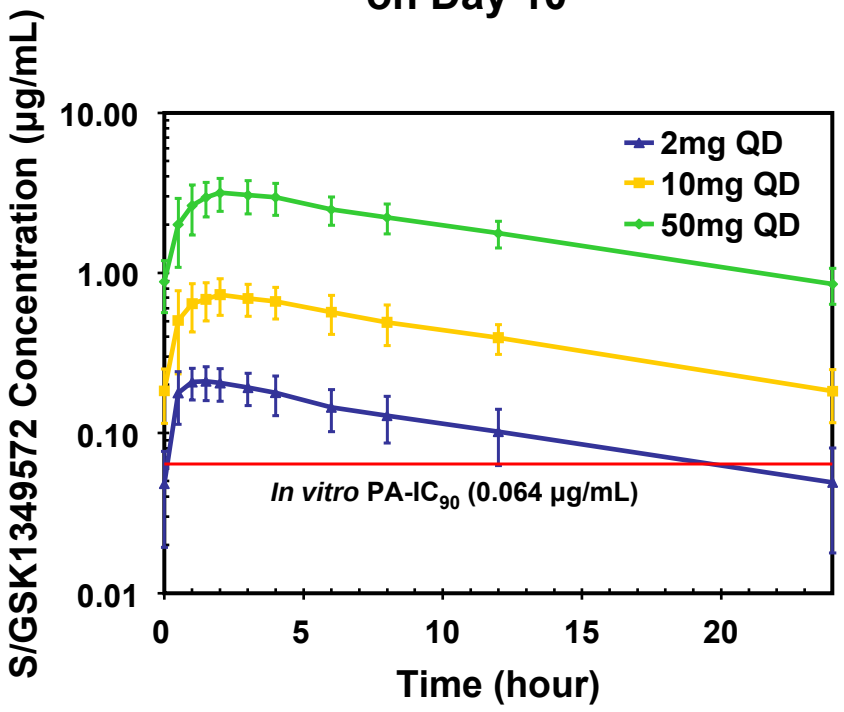
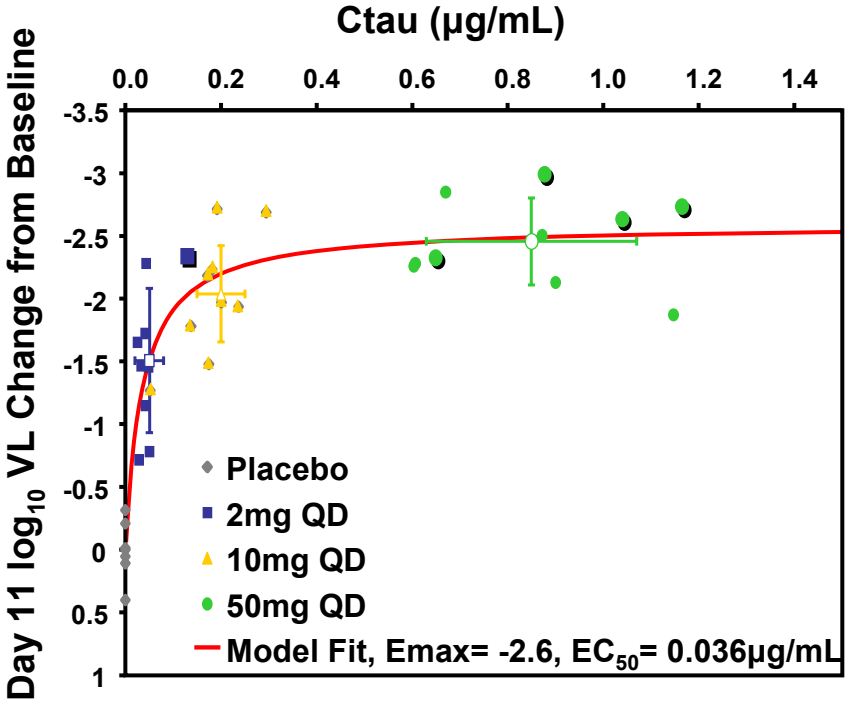
Low Variability in Exposure and Predictable Exposure-Response Relationship from Phase IIa[1]

S/GSK1349572 Plasma Concentrations on Day 10



Emax model of S/GSK1349572 Exposure vs. Response



1. Song I, et al. IAS 2009, Cape Town, Wednesday poster #WEPEB250

ING111521 Drug-related Adverse Events (n≥2)

Adverse Event (AE)	S/GSK1349572 Dose				Placebo (n=7)
	2mg (n=9)	10mg (n=9)	50mg (n=10)	All active (n=28)	
Any AE	3 (33%)	3 (33%)	5 (50%)	11 (39%)	5 (71%)
Diarrhea	1 (11%)	1 (11%)	2 (20%)	4 (14%)	3 (43%)
Fatigue	0	0	2 (20%)	2 (7%)	2 (29%)
Abdominal pain	1 (11%)	0	0	1 (4%)	2 (29%)
Flatulence	0	0	0	0 (0%)	2 (29%)
Headache	0	0	2 (20%)	2 (7%)	0

- Majority of AEs Grade 1 in severity
- Four Grade 3: Migraine HA (50mg), nightsweats (PBO), asymptomatic increased lipase (10mg), asymptomatic increase TG (10mg)
- No clinically significant trends in AEs, laboratory, vital sign or ECG values

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Summary Genotypic and Phenotypic Results for Non-PBO Arms

- 19 Genotypes and 18 Phenotypes were available for the Non-PBO arms
- No RAL or ELV signature resistance substitutions were observed during the 10-day monotherapy study
- No S/GSK1349572 resistance associated substitutions[1] were observed during the 10-day monotherapy study
- No significant decrease in S/GSK1349572 susceptibility was observed from Day 1 to Day 11

1. Sato A, et al. IAS 2009, Cape Town, Wednesday poster #WEPEA097.

S/GSK1349572 Summary

- S/GSK1349572 was generally well-tolerated with short-term dosing in HIV-infected subjects
- Unprecedented antiviral activity
  - 2.5 $\log_{10}$ decline in HIV RNA after 10-day monotherapy with 50mg
  - No S/GSK1349572, RAL or ELV resistance substitutions were observed during the 10-day monotherapy study
- Only once daily, unboosted INI in clinical development
  - Long plasma half life (~15 hrs)
  - Consistent pharmacokinetics (low variability)
  - Clear and predictable exposure-response relationship
- Data support long-term clinical studies in HIV patients
  - Phase IIb studies commencing this month

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