

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

Jay Lalezari, Louis Sloan, Edwin DeJesus, Trevor Hawkins, Lewis McCurdy,
Ivy Song, Julie Borland, Richard Stroder, Shuguang Chen, Yu Lou,
Mark Underwood, Tamio Fujiwara, Stephen Piscitelli, Sherene Min

ING111521 Investigators, GlaxoSmithKline, RTP, NC, USA,
Shionogi & Co., Ltd., Osaka, Japan



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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 RNA¹
- **INI are amongst best tolerated ARVs on market**
 - In studies of treatment-experienced patients, AE rates were comparable to placebo¹
 - In studies of treatment-naïve patients, the proportion of subjects reporting AEs were lower than with EFV²

1. Steigbigel RT. *NEJM* 2008; 359:339-54.

2. Lennox J. ICAAC/IDSA 2008, Wash DC, Abstract H-896a.



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



S/GSK1349572 Key Characteristics

- **Pharmacokinetics**

- Once daily dosing ($t_{1/2}$ =15 hrs), low milligram dose¹
- Low PK variability^{1,2}
- Predictable exposure-response relationship²
- No significant food effect¹
- No CYP induction or inhibition¹

- **Unique resistance profile**

- Limited cross-resistance to raltegravir and elvitegravir^{3,4}
- Potential for higher genetic barrier to resistance³

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.



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/mm³
 - 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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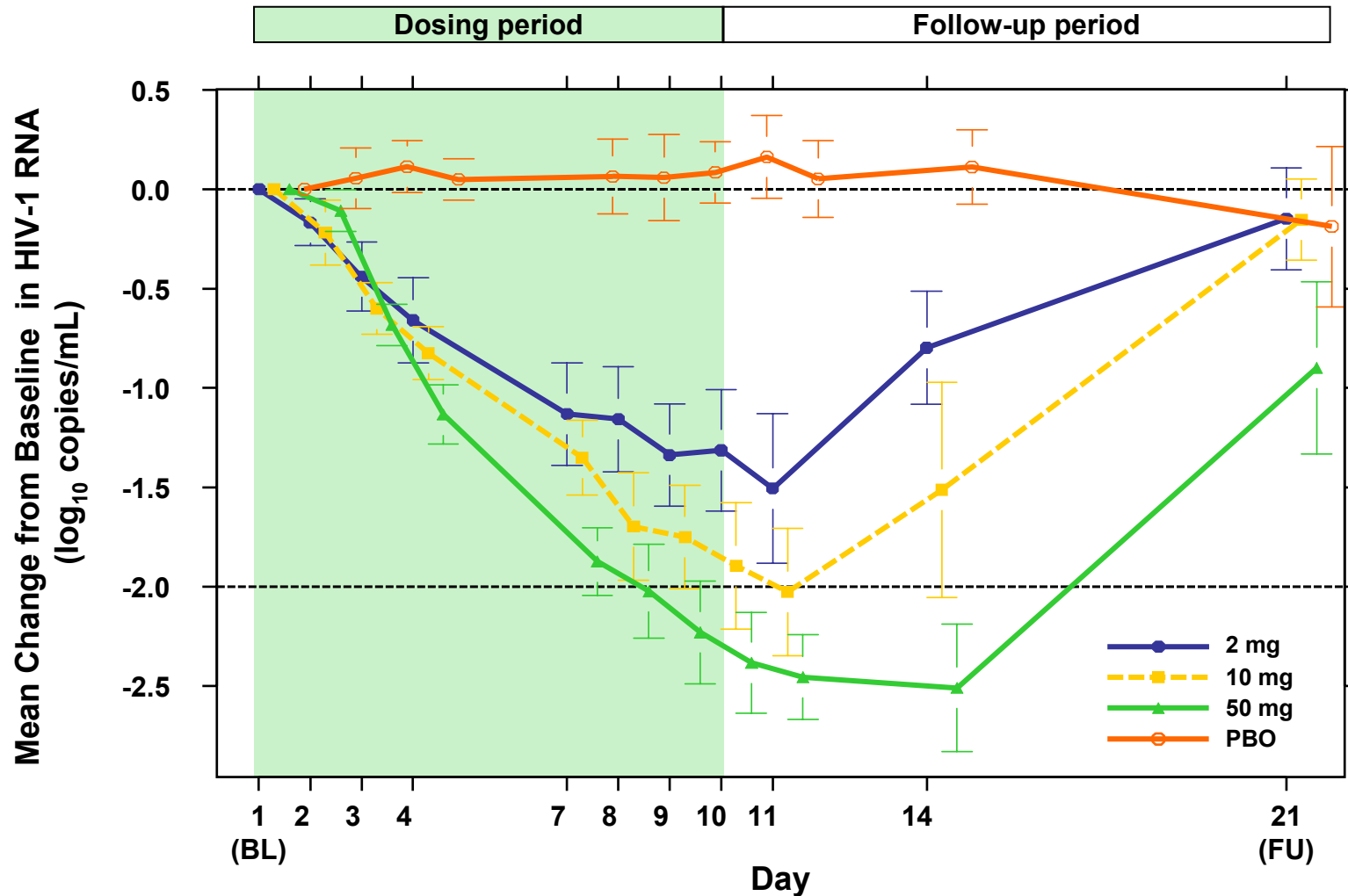
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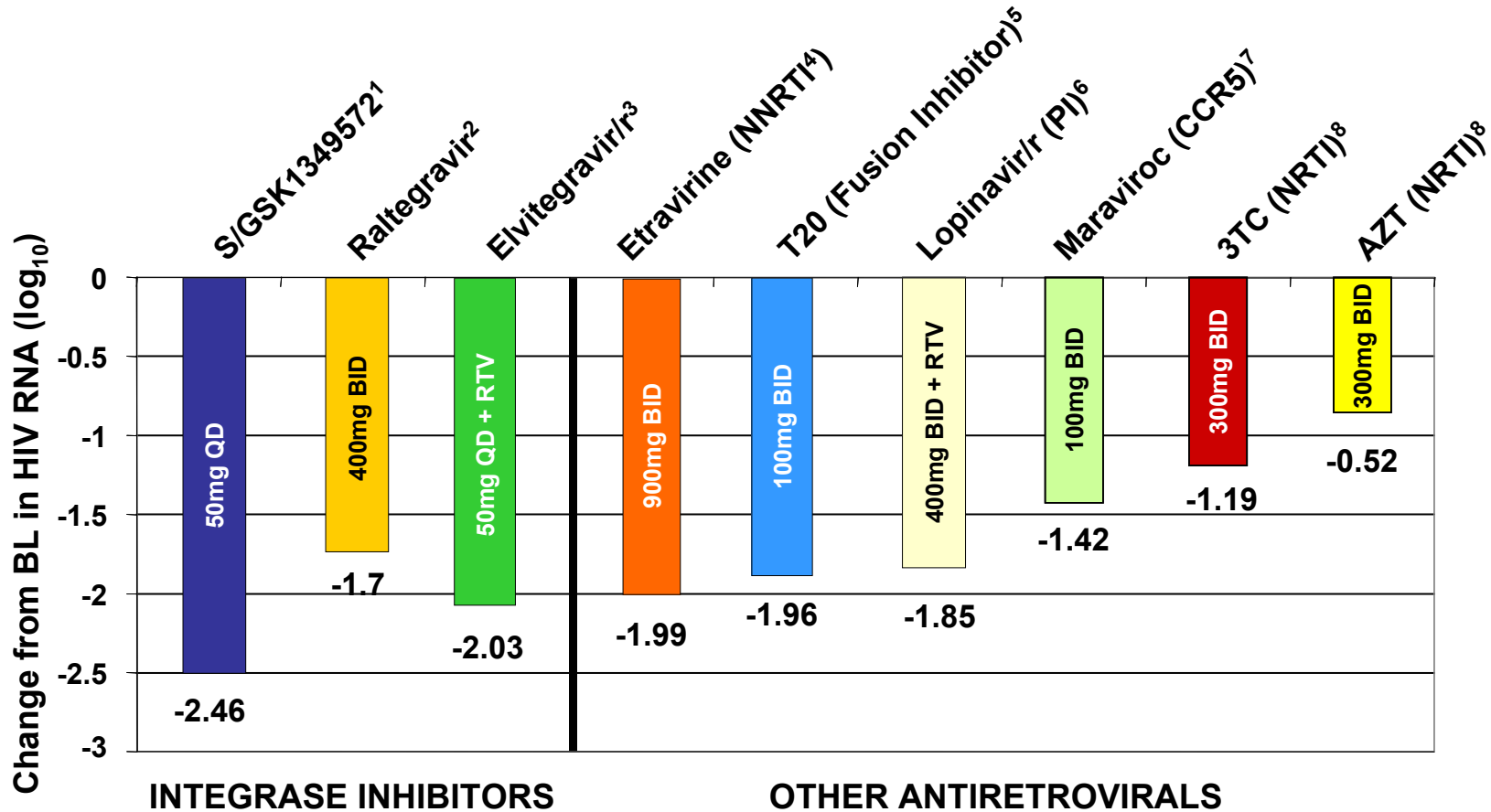
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S/GSK1349572: Unprecedented Antiviral Activity



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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

HIV RNA	S/GSK1349572 Dose		
	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%)

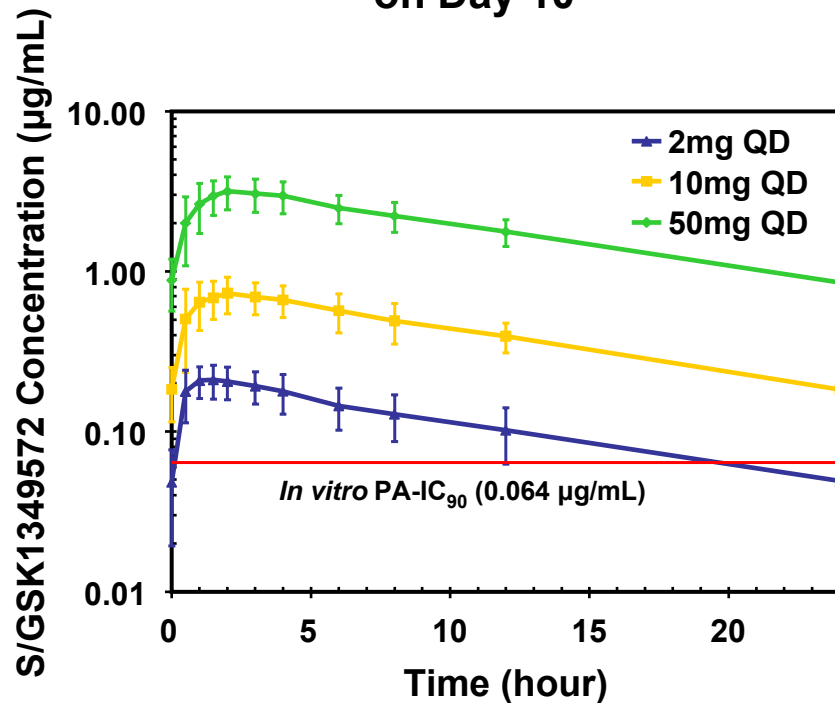
Median CD4 Change to Day 11

	S/GSK1349572 Dose			
	2mg	10mg	50mg	Placebo
Baseline CD4 (cells/mm³) (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)

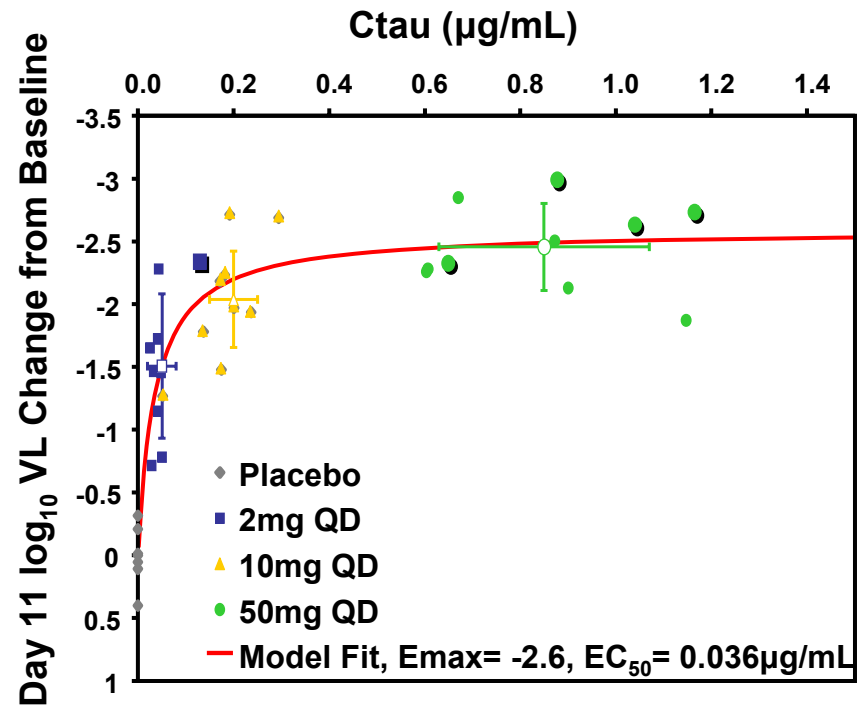


Low Variability in Exposure and Predictable Exposure-Response Relationship from Phase IIa¹

**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

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ING111521 Drug-related Adverse Events (n≥2)

Adverse Event (AE)	S/GSK1349572 Dose				
	2mg (n=9)	10mg (n=9)	50mg (n=10)	All active (n=28)	Placebo (n=7)
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 substitutions¹ 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.

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S/GSK1349572 Summary

- **S/GSK1349572 was generally well-tolerated with short-term dosing in HIV-infected subjects**
- **Unprecedented antiviral activity**
 - 2.5 log₁₀ 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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ING111521 Protocol Study Team

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