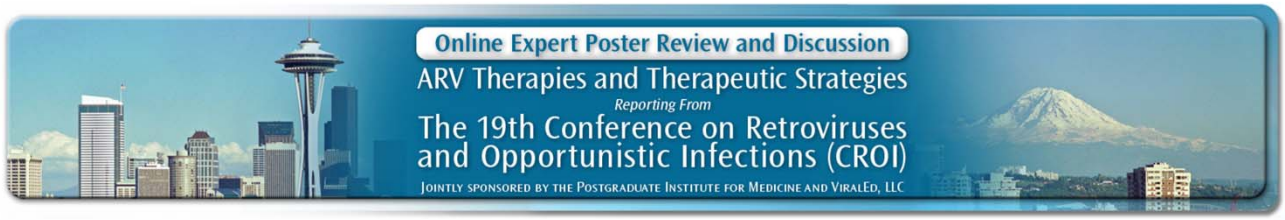


Dolutegravir (DTG; S/GSK1349572) in Combination Therapy Exhibits Rapid and Sustained Antiviral Response in Antiretroviral-Naïve Adults: 96-Week Results from SPRING-1 (ING112276)

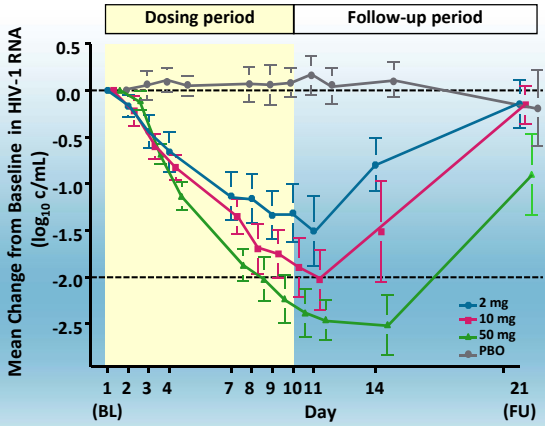
Hans-Juergen Stellbrink,[1] Jacques Reynes,[2] Adriano Lazzarin,[3] Eugene Voronin,[4] Federico Pulido,[5] Franco Felizarta,[6] Steve Almond,[7] Marty St. Clair,[8] Nancy Flack,[8] and Sherene Min,[8] on behalf of the extended SPRING-1 Team

[1]ICH Study Center, Hamburg, Germany; [2]Hopital Gui de Chauliac, Montpellier, France; [3]Fondazione Centro San Raffaele del Monte Tabor, Milano, Italy; [4]Hospital of Infectious Diseases, St. Petersburg, Russia; [5]Hospital 12 Octubre, Madrid, Spain; [6]Office of Franco Felizarta, [7]Bakersfield, CA; [8]GlaxoSmithKline, [7]Mississauga, Canada, [8]Research Triangle Park, NC, USA

Abstract #102LB

Dolutegravir Attributes

- Once daily, unboosted[1]
- Low PK variability and predictable exposure-response relationship[2]
- Low potential for drug interactions[2]
- Improved *in vitro* resistance profile including higher genetic barrier to resistance[3]
- Highly potent antiviral activity in monotherapy[1]
  - At 50mg DTG, 90% were <400 c/mL and 70% <50 c/mL after 10d of monotherapy

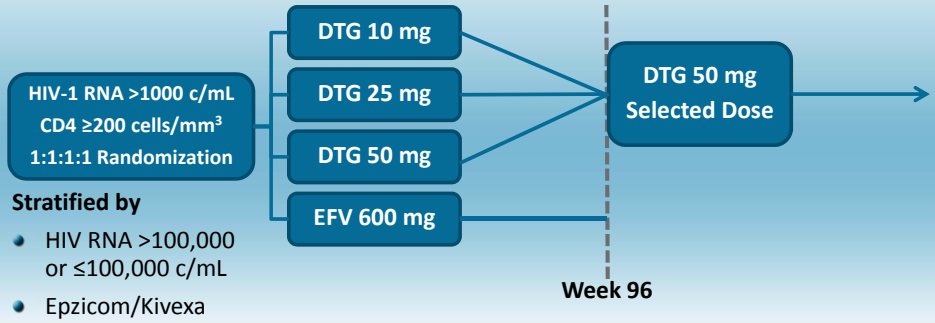


1. Min, S. et al. AIDS. 2011; 25:1737–1745.
2, Min, S. et al. AAC. 2010; 54: 254–258.
3. Kobayashi, M et al. AAC. 2011; 55(2):813-821.

Stellbrink HJ et al. 19th CROI; Seattle, WA; March 5-8, 2012; Abst. 102LB.

ING112276 Study Design

- Phase IIb dose-ranging, partially blinded, N~200 ART-naïve patients
- All arms include 2 NRTI backbone given once daily
- Primary endpoint: % <50 c/mL at 16 weeks (TLOVR), for Ph3 dose selection
- Planned analysis: % <50 c/mL at 96 weeks (TLOVR)



Stratified by

- HIV RNA >100,000 or ≤100,000 c/mL
- Epzicom/Kivexa or Truvada

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Baseline Characteristics

	DTG 10 mg (N=53)	DTG 25 mg (N=51)	DTG 50 mg (N=51)	EFV 600 mg (N=50)	Total (N=205)
Age, median (range), years	32 (21-61)	38 (20-64)	37 (22-55)	40 (20-79)	37 (20-79)
Male gender	42 (79%)	46 (90%)	45 (88%)	44 (88%)	177 (86%)
Race					
African American/African heritage	7 (13%)	6 (12%)	8 (16%)	4 (8%)	25 (12%)
White	41 (77%)	42 (82%)	38 (75%)	43 (86%)	164 (80%)
Other	5 (10%)	3 (6%)	5 (10%)	4 (8%)	17 (8%)
Baseline HIV-1 RNA					
Mean (log_{10} c/mL)	4.42	4.38	4.58	4.46	4.46
>100,000 c/mL	11 (21%)	10 (20%)	12 (24%)	11 (22%)	44 (21%)
Baseline CD4+ (cells/mm³)					
Mean	309.4	333.8	327.2	327.5	324.3
<300	30 (57%)	20 (39%)	24 (47%)	24 (48%)	98 (48%)
Investigator-selected NRTIs					
TDF/FTC	36 (68%)	34 (67%)	34 (67%)	34 (68%)	138 (67%)
ABC/3TC	17 (32%)	17 (33%)	17 (33%)	16 (32%)	67 (33%)

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Primary Outcomes: <50 c/mL (TLOVR) at Week 96

Outcome	DTG 10 mg (N=53)	DTG 25 mg (N=51)	DTG 50 mg (N=51)	EFV 600 mg (N=50)
Responder	42 (79%)	40 (78%)	45 (88%)	36 (72%)
Virologic nonresponders				
Rebound by TLOVR	7 (13%)	4 (8%)	2 (4%)*	4 (8%)
Re-suppressed by Week 96	3	2	1	3
Other nonresponders				
Adverse event	0	1 (2%)	1 (2%)	5 (10%)
Protocol deviation	1 (2%)	2 (4%)	1 (2%)	0
Subject reached protocol-defined stopping criteria	0	0	0	1 (2%)
Lost to follow-up/decision by subject	2 (4%)	3 (6%)	2 (4%)	2 (4%)
Death	1 (2%)**	0	0	0
Not discontinued but no data at Week 96 and beyond	0	1 (2%)	0	2 (4%)

*Includes one subject discontinued from study drug due to Burkitt's lymphoma prior to retest
**By motor vehicle accident

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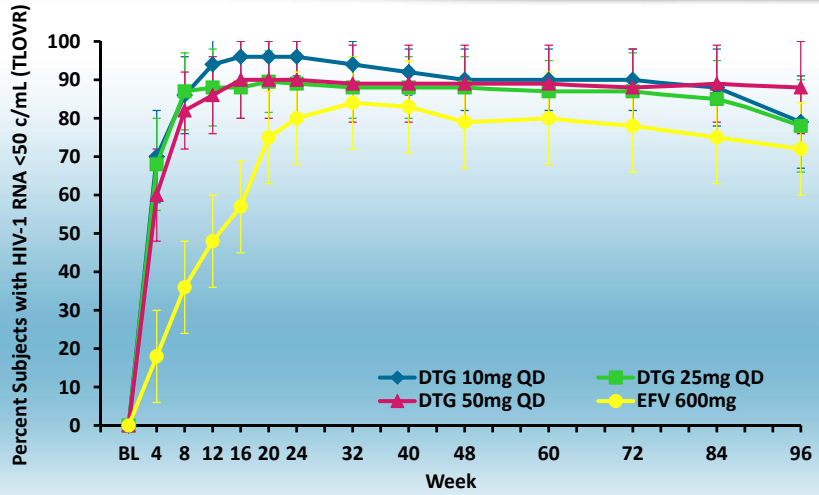
Dolutegravir: Rapid and Durable Antiviral Activity Week 96 Efficacy Analysis (<50 c/mL)



95% confidence intervals are derived using the normal approximation.

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Protocol Defined Virologic Failure

- PDVF = confirmed HIV-1 RNA >400 c/mL OR < 1.0 $\log_{10}$ c/mL decrease by Week 4
- Amongst DTG-treated subjects (N=155), no integrase mutations were detected through Week 96
- No subjects in 50 mg arm had confirmed VL ≥400 c/mL through Wk 96

Outcome	DTG 10mg (N=53)	DTG 25mg (N=51)	DTG 50mg (N=51)	EFV 600mg (N=50)
Protocol-defined Virologic Failure	2 *	1 *	0	1**
Genotype/phenotype Determinable	2	0	0	1
INI Mutations Present	0	0	0	0
NNRTI Mutations Present	0	0	0	0
NRTI Mutations Present	M184V (1)	0	0	0

*Non-adherence in DTG 10mg (n=1) and DTG 25mg subjects by report/pill count at time of PDVF
**<1.0 log10 decrease by Wk 4

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AEs (by System Organ Class) Reported in >1 Subject on Investigational Product

	DTG 10 mg (N=53)	DTG 25 mg (N=51)	DTG 50 mg (N=51)	DTG Subtotal (N=155)	EFV 600 mg (N=50)
Number of Subjects with any Grade 2-4 Drug-Related Event	**4 (8%)**	**5 (10%)**	**8 (16%)**	**17 (11%)**	**12 (24%)**
Gastrointestinal	1 (2%)	2 (4%)	1 (2%)	**4 (3%)**	**2 (4%)**
Psychiatric disorders	0	0	0	**0**	**3 (6%)**
Metabolic disorders	0	3 (6%)	1 (2%)	**4 (3%)**	**0**
Skin disorders	0	0	0	**0**	**3 (6%)**
Infections	2 (4%)	0	0	**2 (1%)**	**0**
General disorders	1 (2%)	1 (2%)	1 (2%)	**3 (2%)**	**1 (2%)**
Laboratory Abnormalities	0	1 (2%)	1 (2%)	**2 (1%)**	**1 (2%)**
Nervous system disorders	0	0	1 (2%)	**1 (<1%)**	**1 (2%)**
Serious Adverse Events (all)	5 (9%)	5 (10%)	7 (14%)	**17 (11%)**	**7 (14%)**
AEs Leading to WD/IP Discontinuation	1 (2%)	1 (2%)	2 (4%)	**4 (3%)**	**5 (10%)**

- Fewer AEs leading to withdrawal on DTG vs EFV:
  - DTG (4/155, 3%): dyspepsia, Burkitt's lymphoma, death due to motor vehicle accident, lipoatrophy
  - EFV (5/50, 10%): abnormal dreams, suicide attempt, drug intolerance, drug hypersensitivity, insomnia

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Laboratory Results: ALT and Bilirubin

Maximum Treatment Emergent Toxicity	DTG 10mg (N=53)	DTG 25mg (N=51)	DTG 50mg (N=51)	DTG Subtotal (N=155)	EFV 600mg (N=50)
Alanine Amino Transferase (ALT)					
Grade 2	1 (2%)	3 (6%)	1 (2%)	5 (3%)	6 (12%)
Grade 3	0	1 (2%)	0	1 (<1%)	0
Grade 4	0	0	0	0	1 (2%)
Total Bilirubin					
Grade 2	0	1 (2%)	1 (2%)	2 (1%)	0
Grade 3	0	0	0	0	0
Grade 4	0	0	0	0	0

- Clinically significant liver chemistry abnormalities were rare
  - 1 Gr3 ALT (DTG 25 mg, Acute HCV infection), 1 Gr4 ALT (EFV, Acute HCV infection)
- No subject with elevated bilirubin had corresponding ALT elevation

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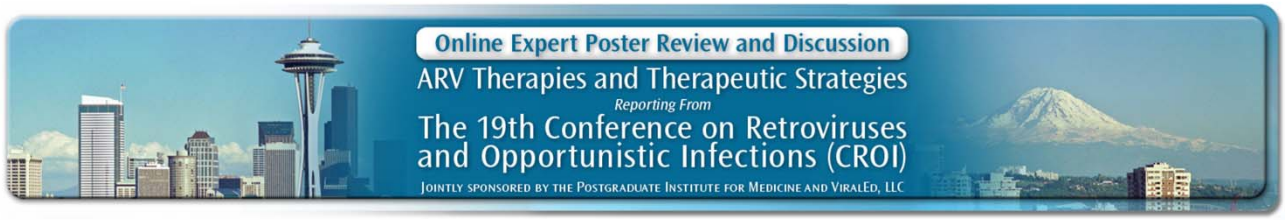
Laboratory Results: Creatinine & Urine Protein

- Small changes in mean serum creatinine (0.1 – 0.15 mg/dL) observed
  - Observed with both NRTI backbones, did not progress over time
  - No effect of DTG on GFR (as measured by iohexol clearance)[1]
- At Week 96, no evidence for higher urine protein in DTG arms

Arm	n (Wk 96)	Mean Urine Alb/Cr ratio (mg/mmol Cr) at Wk96 (SD)	Min/Max
DTG 10mg	38	1.06 (1.699)	0.2 / 9.4
DTG 25mg	33	0.91 (0.95)	0.3 / 5.2
DTG 50mg	38	0.97 (1.113)	0.3 / 6.2
EFV 600mg	34	1.56 (2.908)	0.2 / 16.3

In vitro and clinical data are consistent with non-significant inhibition of the renal transporter (OCT2) responsible for tubular secretion of creatinine

[1]Koteff J, et al. 51st ICAAC; September 17-20, 2011: Chicago, Illinois. Abstract A1-1728.

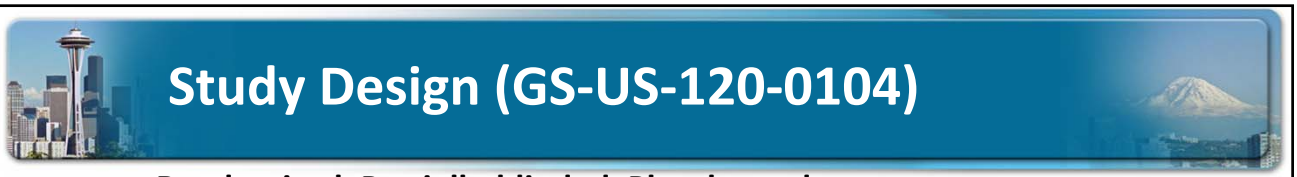


GS-7340 25 mg and 40 mg Demonstrate Greater Antiviral Activity Compared with TDF 300 mg in a 10-Day Monotherapy Study of HIV-1 Infected Patients

PJ Ruane[1], E DeJesus[2], D Berger[3], M Markowitz[4], UF Bredeek[5], C Callebaut[6], L Zhong[6], S Ramanathan[6], MS Rhee[6], K Yale[6]

[1]Peter J Ruane MD Inc., Los Angeles, CA; [2]Orlando Immunology Center, Orlando, FL; [3]Northstar Healthcare, Chicago, IL; [4]Aaron Diamond AIDS Research Center, New York, NY; [5]Metropolis Medical, San Francisco, CA; [6]Gilead Sciences, Foster City, CA

Abstract #103



Study Design (GS-US-120-0104)

Randomized, Partially-blinded, Placebo and Active Controlled 10-day Monotherapy Study

Treatment-naïve and experienced
No genotypic resistance to TDF
HIV-1 RNA ≥ 2,000 c/mL
CD4 ≥ 200 cells/mm³
(N = 36)

- **TDF 300 mg QD**
- **GS-7340 8 mg QD**
- **GS-7340 25 mg QD**
- **GS-7340 40 mg QD**
- **GS-7340 Placebo QD**

- **Primary Objective**
  - To evaluate the antiviral activity of 3 lower doses of GS-7340
- **Primary Endpoint**
  - Time-weighted average change in HIV-1 RNA ($DAVG_{11}$)

Ruane PJ et al. 19th CROI; Seattle, WA; March 5-8, 2012; Abst. 103.

Baseline Characteristics

Treatment Group	All Subjects (n=38)
Age (mean)	38
Sex (males)	97%
Race	
White	53%
African American	37%
Others	11%
Median HIV-1 RNA (log_{10} c/mL)	4.6
Median CD4 cell count (cells/mm^3)	444

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Primary Efficacy Endpoint

Treatment Group	N	Median $DAVG_{11}$ [log_{10} c/mL]	*P* value vs. TDF 300 mg
Placebo	7	-0.01	0.038
TDF 300 mg	6	-0.48	-
GS-7340 8 mg	9	-0.76	0.216
GS-7340 25 mg	8	-0.94	0.017
GS-7340 40 mg	8	-1.08	0.01

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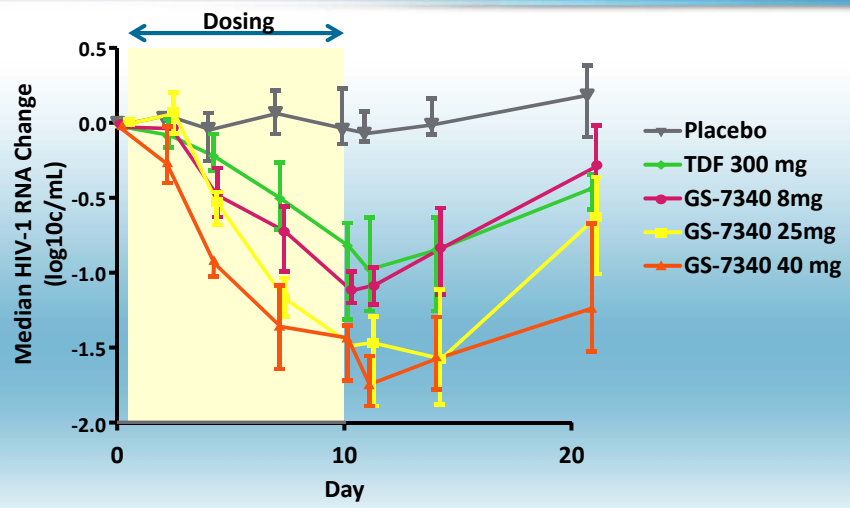
Viral Dynamics



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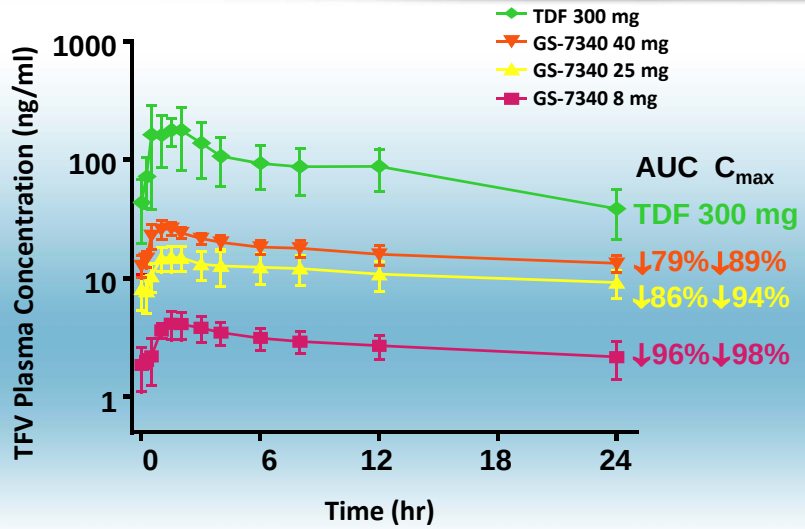
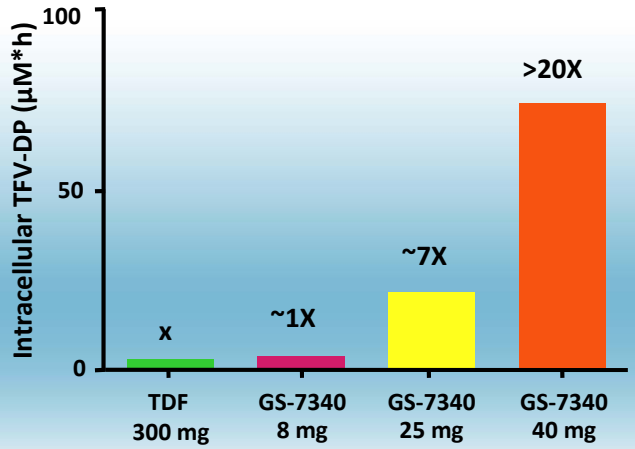
GS-7340: Lower Plasma TFV



Ruane PJ et al. 19th CROI; Seattle, WA; March 5-8, 2012; Abst. 103.

GS-7340:
Higher Intracellular (PBMC) TFV-DP



Ruane PJ et al. 19th CROI; Seattle, WA; March 5-8, 2012; Abst. 103.

Safety and Viral Resistance

- No study drug discontinuations
- No drug-related serious adverse events
- No clinically significant laboratory abnormalities
- Most adverse events were mild to moderate
- No mutations associated with TDF resistance

Ruane PJ et al. 19th CROI; Seattle, WA; March 5-8, 2012; Abst. 103.