Investigational Antiretroviral Drugs and Strategies

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Financial Relationships With Ineligible Companies (Formerly Described as Commercial Interests by the ACCME) Within the Last 2 Years:

Dr Benson has received research grants paid to her through her institution from Gilead Sciences, Inc. (Updated 11/03/21)

Slide 2

Learning Objectives

After attending this presentation, learners will be able to:

- Describe new and novel ARVs in development
- Describe how new or novel ARVs are currently being deployed in new treatment strategies for HIV

Slide 3

US DHHS & IAS-USA Guidelines: Recommended Regimens for First-line ART in Patients With HIV Infection

Class	DHHS[1]	IAS-USA[2]
INSTI	▪ BIC/TAF/FTC* ▪ DTG/ABC/3TC* ▪ DTG/TAF or TDF/FTC or 3TC ▪ DTG/3TC*	▪ BIC/TAF/FTC* ▪ DTG/TAF or TDF/FTC or 3TC ▪ DTG/3TC*

*Single-tablet regimens.

- Recommendations are adjusted based on baseline HIV-1 RNA, CD4+ cell count, CrCl, eGFR, HLA-B*5701 status, HBsAg status, osteoporosis status, and pregnancy status or intent
- No currently recommended first-line regimens contain a pharmacologic-boosting agent
- All options now available QD

1. DHHS ART. Guidelines. August 2021.; 2. Saag. JAMA. 2020;324:1651-69:379.

Available First-line Single-Tablet Regimens

Agent	Components	Caveats
INSTI regimens		
BIC/TAF/FTC	INSTI + dual NRTI	
DTG/ABC/3TC	INSTI + dual NRTI	Only if HLA-B*5701 neg
EVG/COBI/TDF/FTC EVG/COBI/TAF/FTC	INSTI + booster + dual NRTI	
NNRTI regimens		
DOR/3TC/TDF	NNRTI + dual NRTI	No restriction on baseline HIV-1 RNA or CD4+ cell count
EFV/FTC/TDF EFV/TDF/3TC, EFV_{400}mg/TDF/3TC	NNRTI + dual NRTI	
RPV/FTC/TDF RPV/FTC/TAF	NNRTI + dual NRTI	Only if HIV-1 RNA < 100,000 copies/mL and CD4+ cell count > 200 cells/mm^3
Boosted PI regimens		
DRV/COBI/FTC/TAF	PI + booster + dual NRTI	

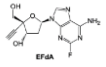
New Antiretroviral Drugs in Development

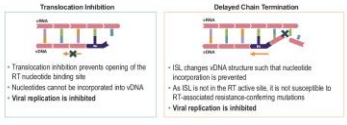
Introduction

- Islatravir
- Lenacapavir
- GSK3640254
- Broadly neutralizing monoclonal antibodies for treatment

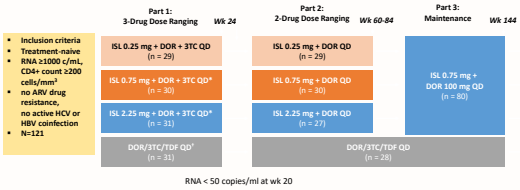
Islatravir (ISL)

- 4'-ethynyl-2-fluoro-2'-deoxyadenosine (MK-8591; EFdA)
- Nucleoside reverse transcriptase translocation inhibitor – chain termination
  - Active at sub-nanomolar concentrations; >10x potency compared with current ARVs
  - Plasma half-life 50-60 hrs; active triphosphate intracellular half-life up to 128 hours
  - Currently under evaluation for both prevention and treatment and in pill and injectable formulations.





Islatravir P011: Phase 2b Study Design



RNA < 50 copies/ml at wk 20

Key findings: 1 Serious drug related AE in the ISL +DOR part 3 arm, No discontinuations for safety events after week 48
Most common AE in ISL + DOR groups: **headache** (6.5%) ; most common AE in DOR/3TC/TDF group: **diarrhea** (19%)
Similar Incidence of both at Weeks 48 and 96

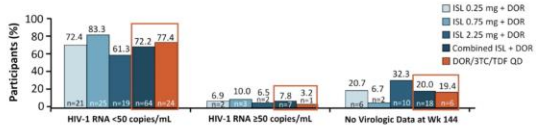
Cunningham, et al. IAS 2021; Abstr OAB0304

Islatravir P011: Efficacy Data at 96 weeks

	ISL (0.25 mg) + DOR QD	ISL (0.75 mg) + DOR QD	ISL (2.25 mg) + DOR QD	ISL Combined	DOR/ 3TC/ TDF QD
	N=29	N=30	N=31	N=90	N=31
Outcome (FDA Snapshot Approach)					
HIV-1 RNA < 50 copies/ mL, n (%)	25 (86.2)	27(90.0)	21(67.7)	73(81.1)	25(80.6)
HIV-1 RNA ≥ 50 copies/ mL, n (%)	2 (6.9)	2 (6.7)	5 (16.1)	9 (10.0)	2 (6.5)
No virologic data at Week 96, n (%)	2 (6.9)	1 (3.3)	5 (16.1)	8 (8.9)	4 (12.9)

Molina JM et al. HIV Glasgow 2020, abstract O415.; Orkin C et al. HIV Glasgow 2020, abstract P047.

Islatravir P011: Week 144 Efficacy Data



- Protocol-defined virologic failure (PDVF, confirmed HIV-1 RNA ≥50 copies/mL) in n = 7 patients
  - All discontinued trial with confirmatory HIV-1 RNA <80 copies/mL
- No instances of clinically significant confirmed viremia (HIV-1 RNA ≥200 copies/mL) or viral drug resistance analysis

Molina. EACS 2021. Abstr OS 1/5.

Slide credit: clinicaloptions.com

Islatravir P011: Week 144 Safety Data

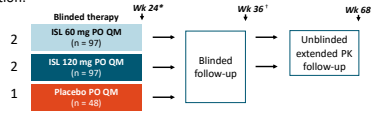
Adverse Event, n (%)	ISL 0.25 mg + DOR* QD (n = 29)	ISL 0.75 mg + DOR* QD (n = 30)	ISL 2.25 mg + DOR* QD (n = 31)	Combined ISL + DOR Groups (n = 90)	DOR/3TC/TDF QD (n = 31)
Drug-related AE	0	3 (10.0)	4 (12.9)	7 (7.8)	7 (22.6)
Serious AE	2 (6.9)	6 (20.0)	2 (6.5)	10 (11.1)	4 (12.9)
Serious drug-related AE	0	0	0	0	1 (3.2)
Discontinued due to AE	1 (3.4)	0	2 (6.5)	3 (3.3)	1 (3.2)
Discontinued due to drug-related AE	0	0	2 (6.5)	2 (2.2)	1 (3.2)

- Most common drug-related AEs were nausea, diarrhea, headache, abnormal dreams
- Lower rate of drug-related AEs in the ISL/DOR arms (7.8%) than DOR/3TC/TDF arm (22.6%)
- All discontinuations due to drug-related AEs occurred before the week 48 time point
- There were no deaths or serious drug-related AEs across any of the ISL/DOR arms

Molina et al. EACS 2021; Abstr OS 1/5

Islatravir Monthly as PrEP: Phase 2a Week 24

- Randomized, double-blind, multicenter, placebo-controlled phase 2a trial
- Study population: HIV-1 negative, age 18-65, low-risk for HIV acquisition (N=242)
- Study randomization:

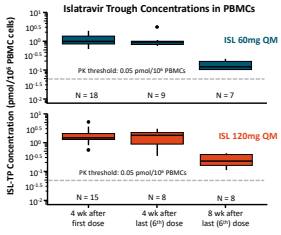


- 1° endpoints: safety/tolerability, pharmacokinetics of ISL-TP (active form of ISL)
- Exploratory endpoints: pharmacokinetics in PBMCs, pharmacokinetics in tissue, hormonal drug-drug interactions

Hillier IAS 2021 #OALC01LB03

Islatravir Monthly as PrEP: Phase 2a Week 24

Results: Pharmacokinetics



Conclusions:
- Generally well-tolerated
- Target thresholds achieved

Phase 3 dose: 60 mg monthly

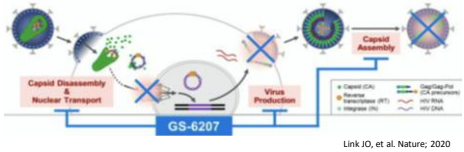
Hillier IAS 2021 #OALC01LB03

Islatravir: Ongoing Clinical Trials

- Phase 3 studies in treatment naïve people (NCT04233879)
- Phase 3 studies in heavily treatment-experienced individuals (NCT04233216)
- Phase 3 trials in PWH with viral suppression who are switching from other regimens (NCT04223778; NCT04223791)
- Phase 2 studies in children and adolescents (NCT04295772)

Lenacapavir (GS-6207): A Novel First in Class Capsid Inhibitor

- Active against a broad range of HIV-1 isolates, including those resistant to current NRTIs, NNRTIs, PIs, and INSTIs
  - Modulates stability and/or transport of capsid complexes; inhibits multiple processes necessary for viral replication
  - Picomolar activity; more potent than current ARVs; oral and SC formulations in development



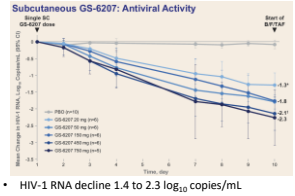
Link JO, et al. Nature; 2020

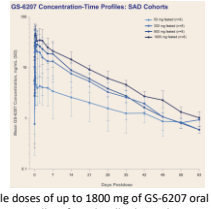
Lenacapavir Resistance Highlights

- Similar activity against all HIV-1 subtypes
- *In vitro* resistance arises at 6 amino acids at the LEN capsid binding site (L56I, **M66I**, Q67H, K70N, K74S/D, T107N)
- Most resistance mutations, except Q67H, correlate with low replication capacity
- Pre-existing LEN mutations have not been found in testing of >1500 HIV-1 clinical isolates
- LEN-resistant HIV-1 isolates are susceptible to HIV protease inhibitors
- LEN is > 20x more active against HIV-2 than HIV-1

Callebaut et al. CROI 2021; Abstr #128

Lenacapavir: 10-Day Antiviral Activity in PWH & PK of Oral Dosing in Healthy Volunteers

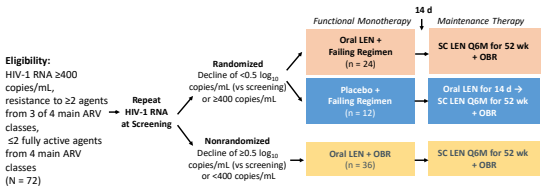




- HIV-1 RNA decline 1.4 to 2.3 $\log_{10}$ copies/mL
- Generally safe and well tolerated
  - Most common AE=ISR; Gr 3-4 AEs→ increased CPK, amylase
- Single doses of up to 1800 mg of GS-6207 oral tablets were generally safe and well tolerated
- $T_{1/2}$ 11-13d, supporting less frequent oral dosing

Daar E, et al. CROI 2020; Abstr. 469; Begley R, et al. CROI 2020; Abstr. 470

CAPELLA: Lenacapavir in Heavily ART-Experienced People



- Primary endpoint achieved in prior analysis: ≥0.5 log_{10} copies/mL decline in HIV-1 RNA at Day 14 in randomized cohort (90% of LEN vs 17% placebo); 1.93 log_{10} reduction in viremia in LEN group in first 14d
- Secondary endpoints: HIV-1 RNA <50 copies/mL, <200 copies/mL at Week 26 in randomized cohort

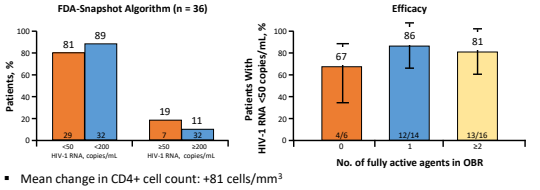
Segal-Maurer CROI 2021; Abstr 127 Molina, et al. IAS 2021; Abstr OALX01LB02

CAPELLA: Baseline Characteristics

Characteristic	Randomized		Nonrandomized	Total (N = 72)
	LEN (n = 24)	Placebo (n = 12)	LEN (n = 36)	
Median age, yr (range)	55 (24-71)	54 (27-59)	49 (23-78)	52 (23-78)
Female at birth, %	29	25	22	25
Black, %	42	55	31	38
Hispanic/Latinx, %	25	36	14	21
Median HIV-1 RNA, log_{10} copies/mL (range) • >75,000 copies/mL, %	4.2 (2.3-5.4) 17	4.9 (4.3-5.3) 50	4.5 (1.3-5.7) 28	4.5 (1.3-5.7) 28
Median CD4+ cell count, cells/mm³ (range) • ≤200 cells/mm³, %	172 (16-827) 67	85 (6-237) 92	195 (3-1296) 53	150 (3-1296) 64
Median time since HIV diagnoses, yr (range)	27 (13-39)	26 (14-35)	23 (9-44)	24 (9-44)
Median prior ARVs, No. (range)	9 (2-24)	9 (3-22)	13 (3-25)	11 (2-25)
Median ARVs in failing regimen, No. (range)	3 (1-7)	3 (2-6)	4 (2-7)	3 (1-7)
Resistance to ≥2 drugs in class, % • NRTI • NNRT • PI • INSTI	 96 92 83 83	 100 100 67 58	 100 100 83 64	 99 97 81 69

Molina. IAS 2021. Abstr OALX01LB02.

CAPELLA Secondary Endpoints: Efficacy at Week 26 in Randomized Cohort



- Mean change in CD4+ cell count: +81 cells/mm³
- Incidence of very low CD4+ cell count (<50 cells/mm³) decreased from 22% (8/36) at baseline to 0% (0/34) at Week 26

Molina. IAS 2021. Abstr OALX01LB02. Reproduced with permission.

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CAPELLA: Emergence of LEN Resistance

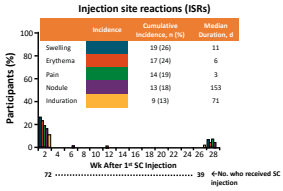
Outcome, n (%)	Randomized Cohort (n = 36)
Patients meeting criteria for resistance testing	**11 (31)**
No emergent LEN resistance	**7 (19)**
Emergent LEN resistance	**4 (11)**
▪ **M66I**	**4**
▪ **Q67H**	**1**
▪ **K70N/R/S**	**1**
▪ **N74D**	**1**

- All 4 patients with emergent LEN resistance remained on LEN
  - 3 patients re-suppressed HIV RNA at a later visit, only 1 had a change in OBR
  - 1 patient with no fully active companion agents never fully suppressed HIV RNA but had a decline of 1.7 $\log_{10}$ copies/mL
- No patients developed additional resistance to OBR agents

Molina. IAS 2021. Abstr OALX01LB02.

CAPELLA: Wk 26 Safety, Injection Site Reactions in Randomized and Nonrandomized Cohorts

Outcome with incidence ≥5%, n (%)	Total (N = 72)
Adverse event	
▪ Diarrhea	6 (8)
▪ Nausea	6 (8)
▪ Cough	5 (7)
▪ Headache	5 (7)
▪ Pyrexia	5 (7)
▪ Urinary tract infection	5 (7)
▪ Abdominal distension	4 (6)
▪ Arthralgia	4 (6)
▪ Back pain	4 (6)
▪ Constipation	4 (6)
▪ Oral candidiasis	4 (6)
▪ Rash	4 (6)
Any grade 3/4 lab abnormality	19 (26)
▪ Low creatinine clearance/high creatinine	8 (11)
▪ Glycosuria	4 (6)
▪ Nonfasting/fasting hyperglycemia	4 (6)



- 56% (40 of 72) had ≥1 ISR related to LEN; 28 grade 1, 2 grade 3, no grade 4
- All 36 patients in randomized cohort received second LEN injection

Molina. IAS 2021. Abstr OALX01LB02.

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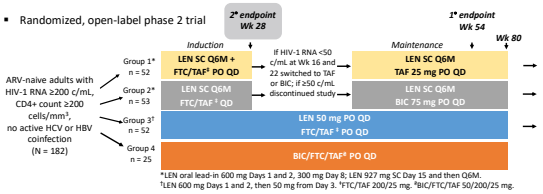
CAPELLA Conclusions: LEN for Treatment of Highly Drug Resistant HIV-1

- Lenacapavir combined with optimized background therapy was effective and safe at Week 26 in heavily treatment-experienced patients with MDR HIV-1 infection
  - Rate of viral suppression 81%
  - Overall, 81 cells/mm^3 increase in CD4+ cell count
    - No patients had CD4+ cell count <50 cells/mm^3 at Week 26 vs 22% at baseline
  - Treatment well tolerated with no AEs leading to discontinuation
  - All randomized patients received second SC lenacapavir injection
- Data support ongoing evaluation of lenacapavir for HIV-1 treatment in heavily treatment-experienced patients with MDR HIV-1 infection
- More information on resistance needed

Molina. IAS 2a021. Abstr OALX01LB02.

CALIBRATE: Lenacapavir in ART-Naïve PLWH

- Randomized, open-label phase 2 trial



*LEN oral lead-in 600 mg Days 1 and 2, 300 mg Day 8; LEN 927 mg SC Day 15 and then Q6M. †LEN 600 mg Days 1 and 2, then 50 mg from Day 3. ‡FTC/TAF 200/25 mg. §BIC/FTC/TAF 50/200/25 mg.

- Participants at baseline: median age 29 yr; 93% male; 52% Black race; 45% Latinx ethnicity
- Primary outcome: proportion with HIV-1 RNA <50 c/mL at Wk 54; **secondary outcomes: proportion with HIV-1 RNA <50 c/mL at Wk 28**, 38, and 80; change from baseline in $\log_{10}$ HIV-1 RNA and CD4+ cell count at Wk 28, 38, 54, and 80

Gupta. IAS 2021. Abstr OALB0302.

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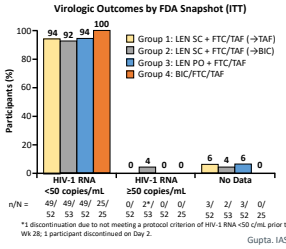
CALIBRATE: Week 28 Virologic Outcomes



*1 discontinuation due to not meeting a protocol criterion of HIV-1 RNA <50 c/mL prior to Wk 28; 1 participant discontinued on Day 2.

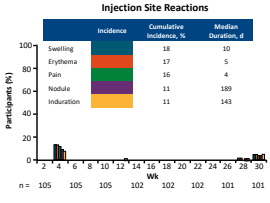
- One participant in **LEN SC + FTC/TAF → BIC** arm had emergent resistance mutations at Wk 10
  - CA: Q67H + K70R (20-fold change for LEN)
  - RT: M184M/I
- Plasma LEN concentrations consistently in target range

Gupta. IAS 2021. Abstr OALB0302.

Slide credit: clinicaloptions.com

CALIBRATE: Adverse Events and Injection Site Reactions

- LEN well tolerated
  - No SAEs or grade 4 AEs related to study drug
  - Most common AEs: headache and nausea (11% each)
  - GI AEs in SC vs oral LEN:
    - Nausea: 12% vs 8%
    - Diarrhea: 6% vs 8%
- ISRs in 39% of pts; 83% were grade 1 and generally resolved in days
- 2 discontinuations due to ISRs (grade 1 injection site induration)



Gupta. IAS 2021. Abstr OALB0302.

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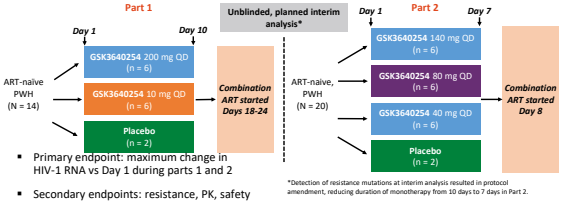
Next Generation Maturation Inhibitor: GSK3640254

- GSK3640254/GSK'254
  - Prevents the proteolytic cleavage of specific portions of the Gag protein which prevents processing of the Gag-Pol polyprotein in late stage of HIV replication.
  - Pre-existing mutations at the cleavage site led to termination of development of an earlier maturation inhibitor (bevirimat).
  - Phase 2a results of a two-part study of GSK '254 presented at CROI 2021.

Phase 2a Study of GSK3640254: Study Design

- Multicenter, randomized, double-blind (sponsor-unblinded), placebo-controlled trial



- Primary endpoint: maximum change in HIV-1 RNA vs Day 1 during parts 1 and 2
- Secondary endpoints: resistance, PK, safety

*Detection of resistance mutations at interim analysis resulted in protocol amendment, reducing duration of monotherapy from 10 days to 7 days in Part 2.

Spinner. CROI 2021. Abstr 126.

Slide adapted from: clinicaloptions.com

Phase 2a Study of GSK3640254: Baseline Characteristics

Characteristic	GSK3640254					Placebo (n = 4)	Total (N = 34)
	10 mg* (n = 6)	40 mg† (n = 6)	80 mg† (n = 6)	140 mg† (n = 6)	200 mg* (n = 6)		
Mean age, yrs (SD)	32.7 (8.3)	27.7 (6.9)	32.8 (6.2)	33.2 (8.2)	29.3 (3.9)	36.5 (9.3)	31.8 (7.2)
Male, n (%)	6 (100)	5 (83)	6 (100)	5 (83)	6 (100)	4 (100)	32 (94)
Mean BMI (SD)	25.3 (3.7)	23.9 (4.3)	24.8 (3.7)	23.4 (1.6)	22.6 (2.2)	23.0 (1.3)	23.9 (3.0)
Race, n (%)							
▪ White	2 (33)	5 (83)	4 (67)	5 (83)	5 (83)	3 (75)	24 (71)
▪ Black	0	1 (17)	2 (33)	1 (17)	0	0	4 (12)
▪ Other	4 (67)	0	0	0	1 (17)	1 (25)	6 (18)
Mean HIV-1 RNA, $\log_{10}$ copies/mL (SD)	4.19 (0.311)	4.67 (0.233)	4.43 (0.510)	4.53 (0.577)	4.82 (0.476)	4.25 (0.417)* 4.25 (0.417)†	4.47 (0.489)* 4.57 (0.592)†

*Part 1. †Part 2.

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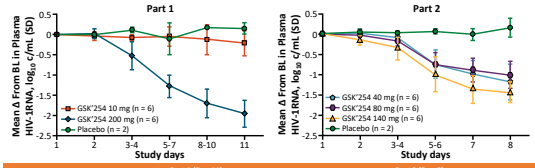
Phase 2a Study of GSK3640254: Antiviral Activity



Mean Change in HIV-1 RNA vs BL, log_{10} copies/mL (SD)	Part 1 (Day 11)			Part 2 (Day 8)			
	GSK3640254 10 mg (n = 6)	GSK3640254 200 mg (n = 6)	Placebo (n = 2)	GSK3640254 40 mg (n = 6)	GSK3640254 80 mg (n = 6)	GSK3640254 140 mg (n = 6)	Placebo (n = 2)
Primary endpoint	-0.22 (0.309)	-1.96 (0.337)	0.14 (0.134)	-1.18 (0.436)	-1.02 (0.330)	-1.45 (0.235)	0.15 (0.226)
Maximum change	-0.36 (0.252)	-2.01 (0.329)	-0.21 (0.262)	-1.18 (0.436)	-1.02 (0.330)	-1.49 (0.267)	-0.03 (0.127)

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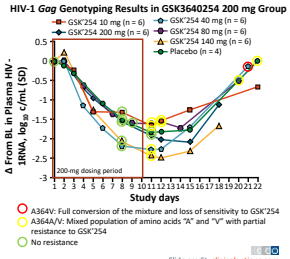
Phase 2a Study of GSK3640254: Resistance

- Resistance mutation A364A/V detected in 4 of 6 patients receiving GSK3640254 200 mg QD at Day 11 in part 1
  - Full conversion and phenotypic resistance in 1 of 4
- No resistance in 10 mg QD group
- Protocol amendment reduced duration of monotherapy from 10 days to 7 days in Part 2
- No resistance detected at any dose in part 2 (140 mg, 80 mg, or 40 mg)



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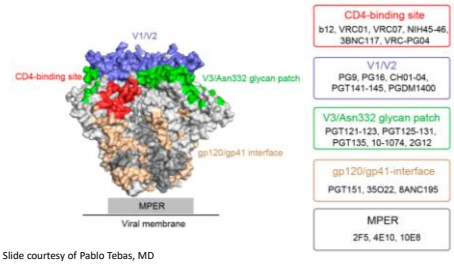
GSK3640254 Conclusions

- In ART-naive persons with HIV, the novel HIV-1 maturation inhibitor, GSK3640254, demonstrated clear dose-response activity
  - HIV-1 RNA decreased 1.5 log_{10} copies/mL with the 140 mg QD dose and 2.0 log_{10} copies/mL with the 200 mg QD dose
- GSK3640254 was well-tolerated
  - No grade 3/4 AEs and no AEs leading to d/c
- These findings support further evaluation of GSK3640254 (100 mg QD, 150 mg QD, and 200 mg QD) in combination with 2 NRTIs in a phase 2b study

Spinner. CROI 2021. Abstr 126.

Broadly Neutralizing Antibodies against HIV



Slide courtesy of Pablo Tebas, MD

Combinations and Approaches in Clinical Trials

- A5357: A single arm trial of long-acting cabotegravir and VRC07LS (a broadly neutralizing antibody; bNAb) as maintenance ART
- A5364: A single arm trial of two bNAbs (3BNC117-LS & 10-1074-LS) to prevent relapse of viremia after discontinuation of oral ART
- A5377: A first-in-human Phase 1 clinical trial of a tri-specific monoclonal antibody (SAR441236) to establish safety, pharmacokinetics, and preliminary antiviral activity
- Ongoing Phase 1 study with GS-5423 (AKA 3BNC117-LS) in people with virologic suppression

Summary

- The pipeline is robust for development of investigational ARVs with unique mechanisms of action and improved activity compared to many first line drugs and regimens
- The promise of novel long-acting injectable drug formulations is their potential for changing the landscape of ART with:
  - Fewer drugs/fewer pills; possibly lower cost; less drug resistance?
- Trials of alternative strategies using cabotegravir in combination with other agents and in populations that struggle with adherence are in progress
  - These may provide insights into novel future use of long-acting injectable drugs.

Thank you for your attention!

Question-and-Answer Session