HIV DRUG THERAPY GLASGOW 2024

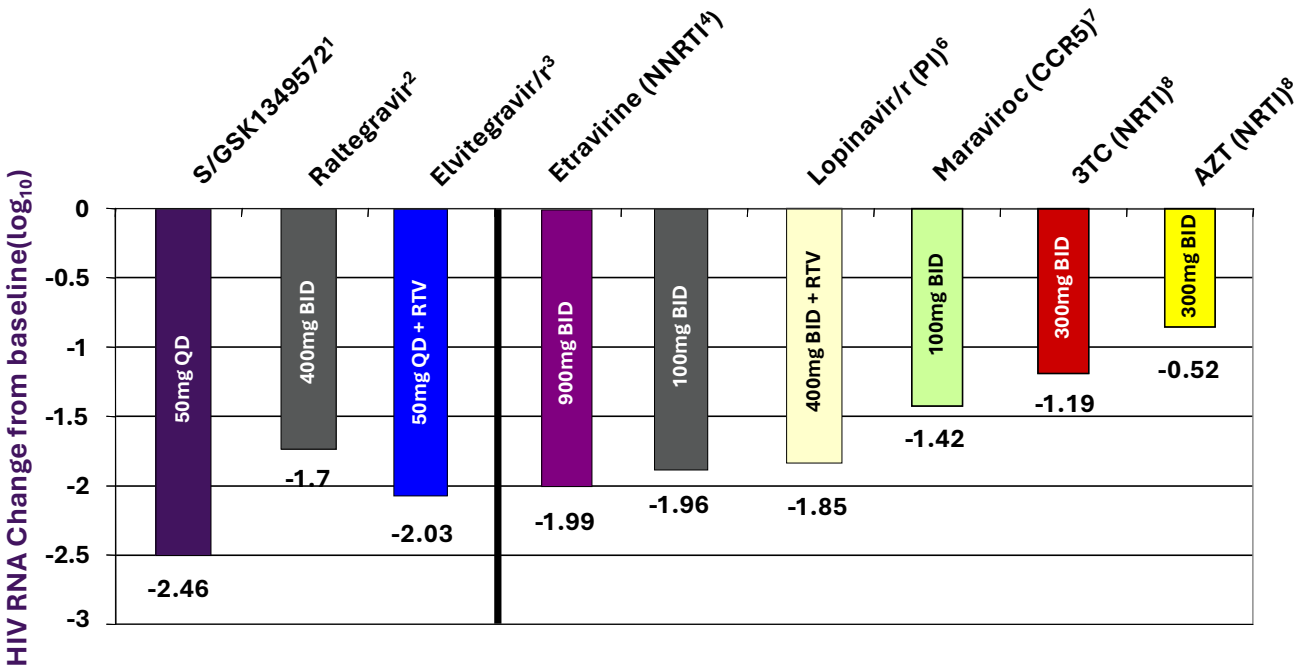
New Treatments and Future Combinations

JOSE R ARRIBAS

SaludMadrid Hospital Universitario La Paz
Hospital Carlos III
Hospital Cantoblanco

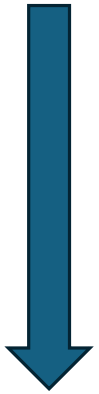
IdiPAZ
Instituto de Investigación
Hospital Universitario La Paz

POTENCY



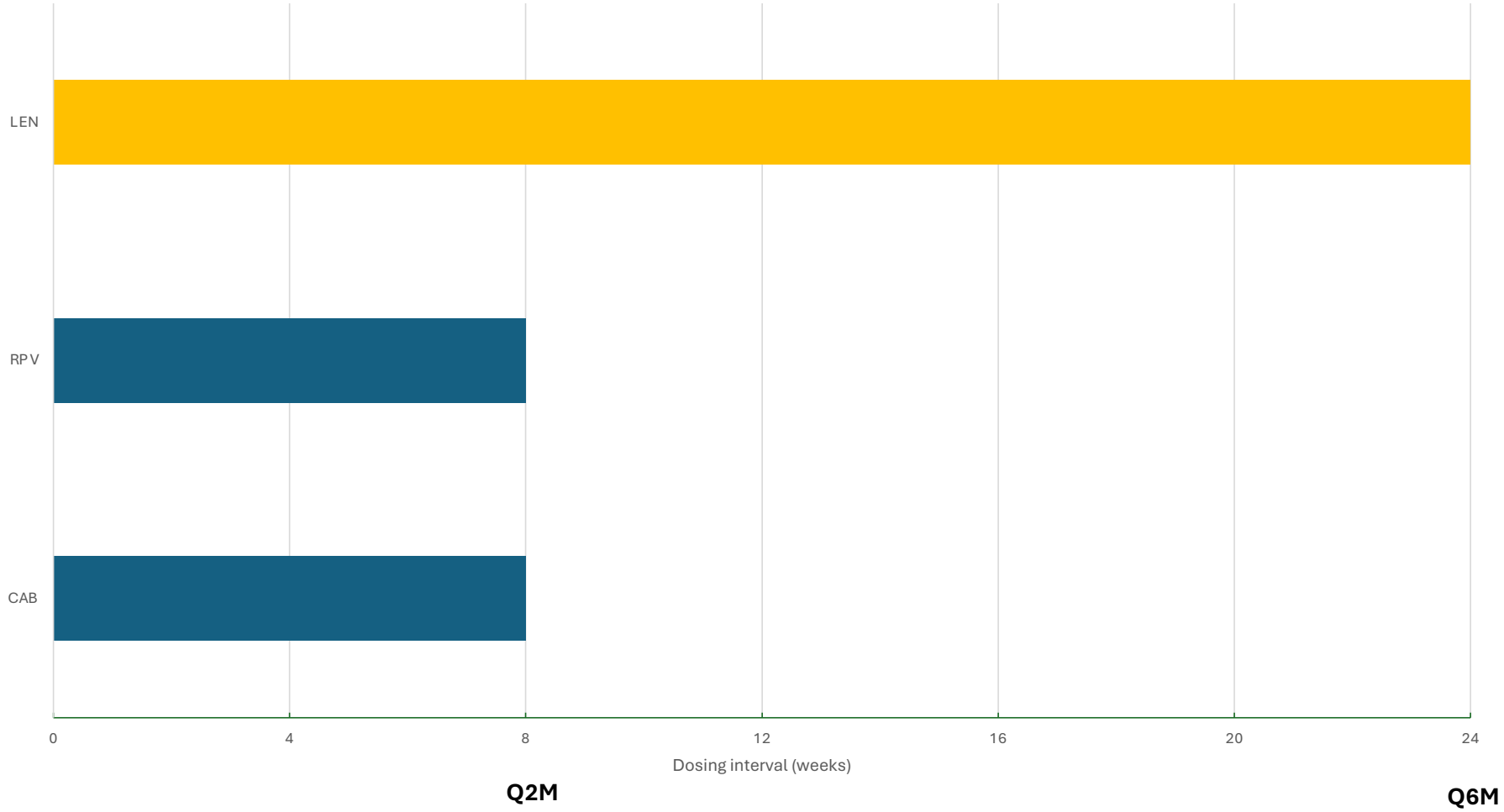
1. Lalezari J. 5th *IAS 2009, Cape Town,* abstract TUAB105.
2. DeJesus E. *J Acquir Immune Defic Syndr* 2006 ; 43:1-5.
3. Markowitz et al. *JAIDS* Volume 43(5) 15 December 2006 pp 509-515.
4. Sankatsing et al. *AIDS* 2003, 17:2623–2627.
5. Kilby JM. AIDS Res Hum Retroviruses 2002; 18:685-694.
6. Murphy 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.

POTENCY & GENETIC BARRIER



-2.5 logs
0 resistance

INTERVAL



INTERVAL

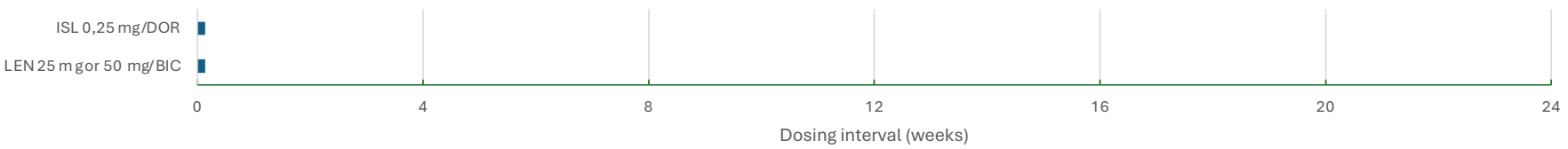
Q2M, Q6M

INTERVAL

Q2M, Q6M
1.4% resistance*

*Orkin C. CID 2023

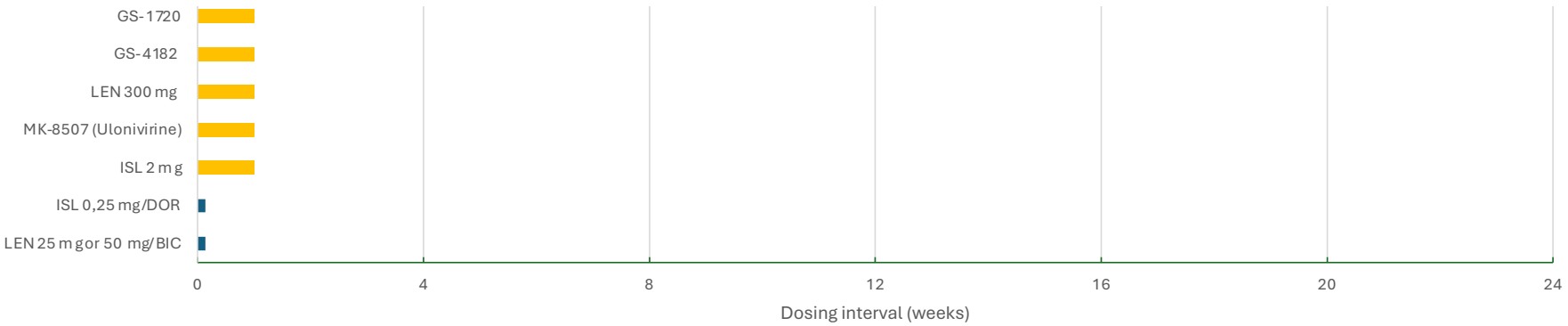
INTERVAL*



QD

*For a number of drugs the interval is aspirational, still under investigation

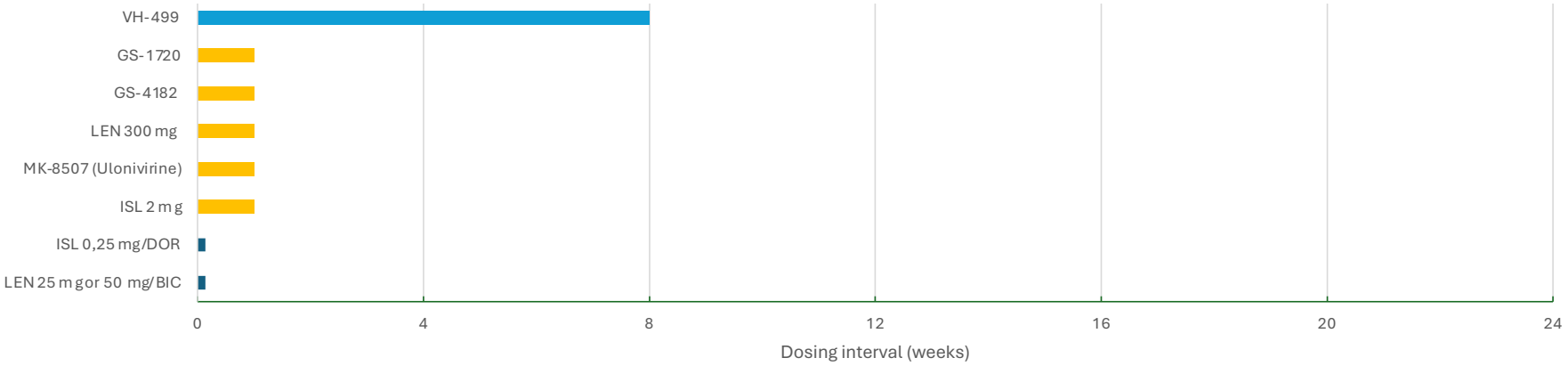
INTERVAL*



QD **QW**

*For a number of drugs the interval is aspirational, still under investigation

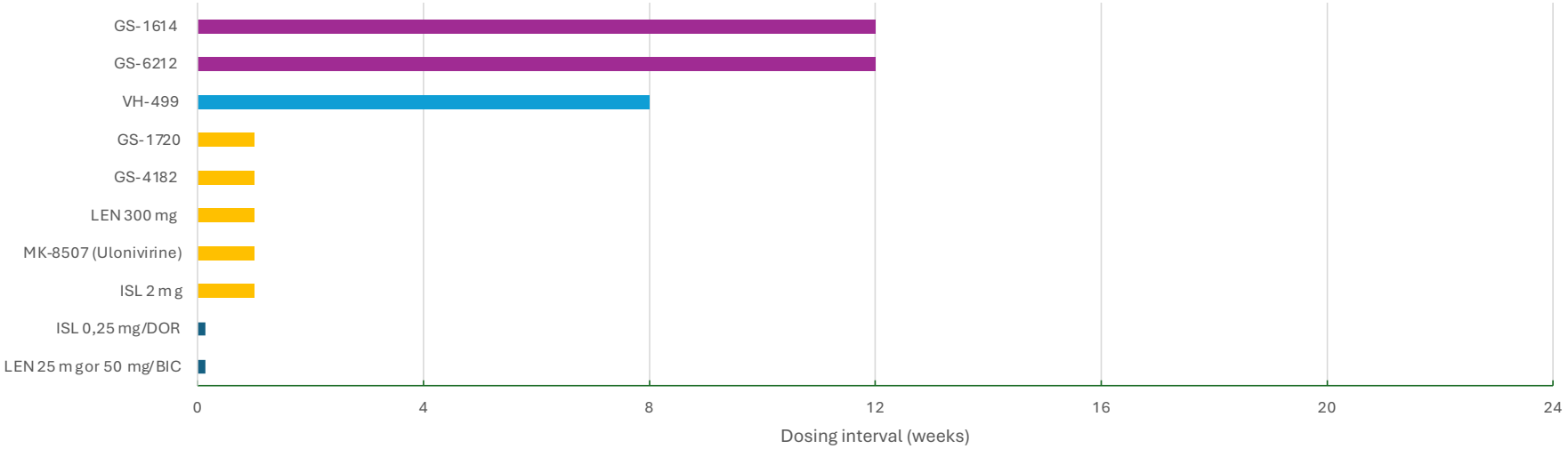
INTERVAL*



QD **QW** **Q2M**

*For a number of drugs the interval is aspirational, still under investigation

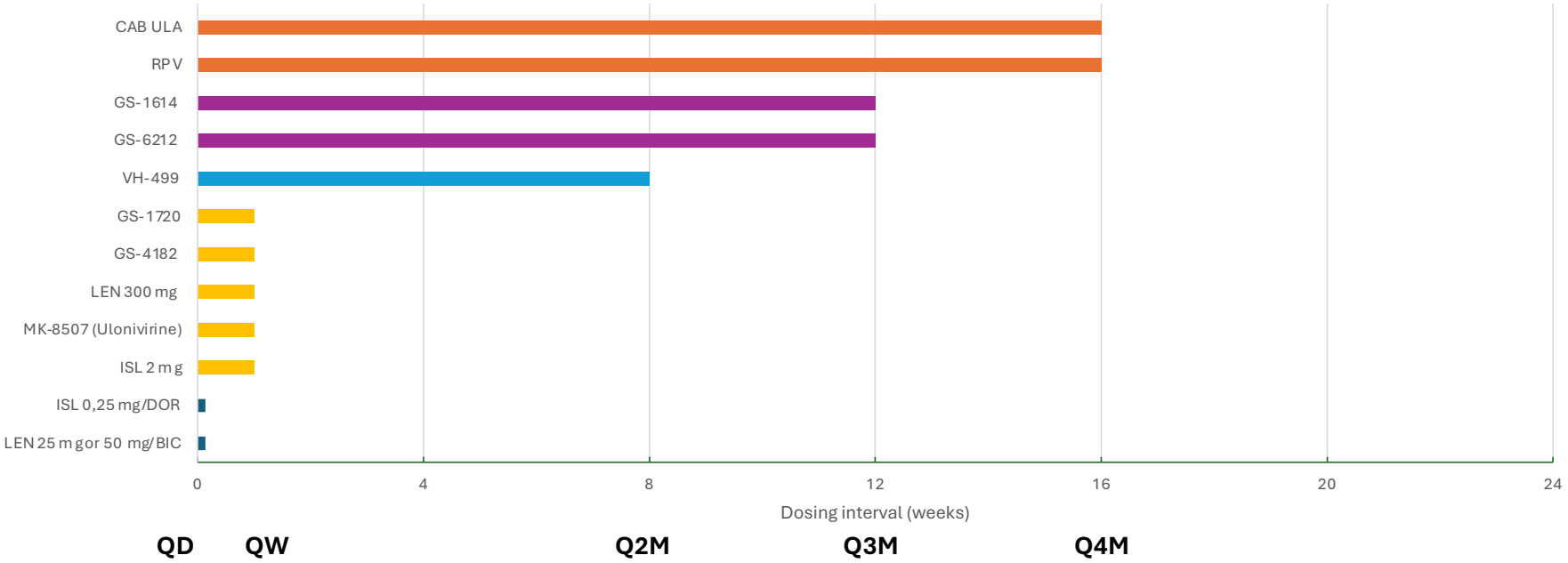
INTERVAL*



QD **QW** **Q2M** **Q3M**

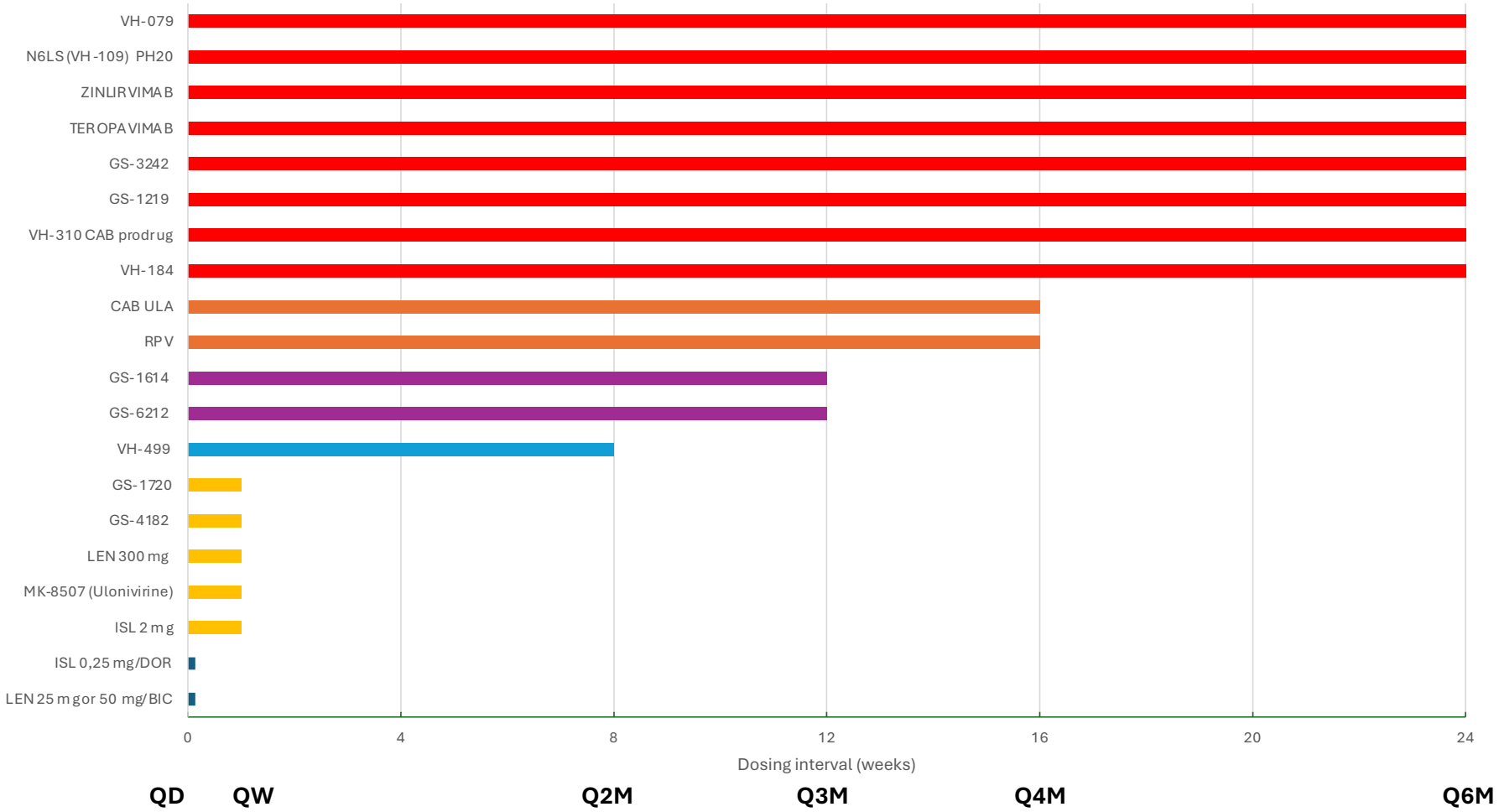
*For a number of drugs the interval is aspirational, still under investigation

INTERVAL*



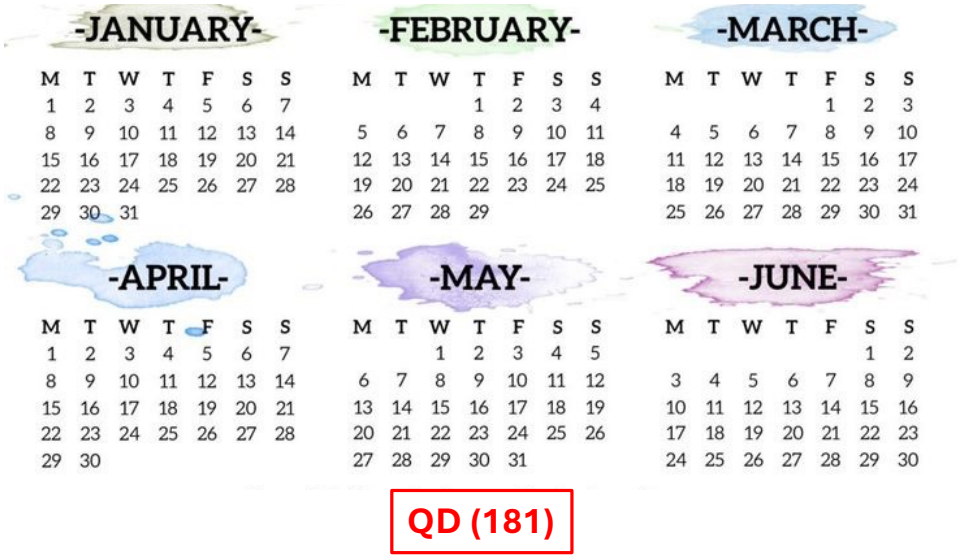
*For a number of drugs the interval is aspirational, still under investigation

INTERVAL*



*For a number of drugs the interval is aspirational, still under investigation

In the next 6 months, how many days will I need to worry about taking my medication?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M T W T F S S
1 2 3 4 5 6 7
8 9 10 11 12 13 14
15 16 17 18 19 20 21
22 23 24 25 26 27 28
29 30 31
-FEBRUARY-
M T W T F S S
1 2 3 4
5 6 7 8 9 10 11
12 13 14 15 16 17 18
19 20 21 22 23 24 25
26 27 28 29
-MARCH-
M T W T F S S
1 2 3
4 5 6 7 8 9 10
11 12 13 14 15 16 17
18 19 20 21 22 23 24
25 26 27 28 29 30 31
-APRIL-
M T W T F S S
1 2 3 4 5 6 7
8 9 10 11 12 13 14
15 16 17 18 19 20 21
22 23 24 25 26 27 28
29 30
-MAY-
M T W T F S S
1 2 3 4 5
6 7 8 9 10 11 12
13 14 15 16 17 18 19
20 21 22 23 24 25 26
27 28 29 30 31
-JUNE-
M T W T F S S
1 2
3 4 5 6 7 8 9
10 11 12 13 14 15 16
17 18 19 20 21 22 23
24 25 26 27 28 29 30

QD (181)


-JANUARY-
M T W T F S S
1 2 3 4 5 6 7
8 9 10 11 12 13 14
15 16 17 18 19 20 21
22 23 24 25 26 27 28
29 30 31
-FEBRUARY-
M T W T F S S
1 2 3 4
5 6 7 8 9 10 11
12 13 14 15 16 17 18
19 20 21 22 23 24 25
26 27 28 29
-MARCH-
M T W T F S S
1 2 3
4 5 6 7 8 9 10
11 12 13 14 15 16 17
18 19 20 21 22 23 24
25 26 27 28 29 30 31
-APRIL-
M T W T F S S
1 2 3 4 5 6 7
8 9 10 11 12 13 14
15 16 17 18 19 20 21
22 23 24 25 26 27 28
29 30
-MAY-
M T W T F S S
1 2 3 4 5
6 7 8 9 10 11 12
13 14 15 16 17 18 19
20 21 22 23 24 25 26
27 28 29 30 31
-JUNE-
M T W T F S S
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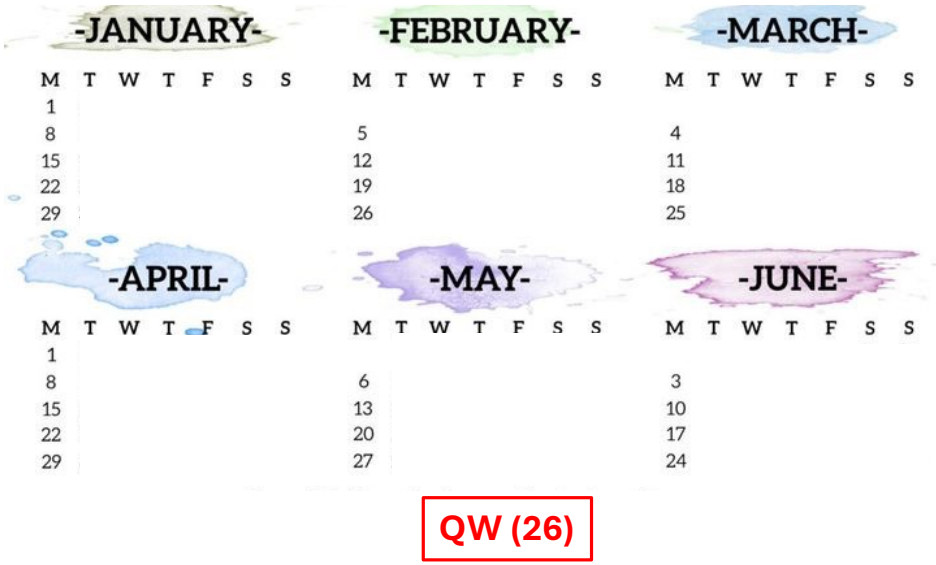
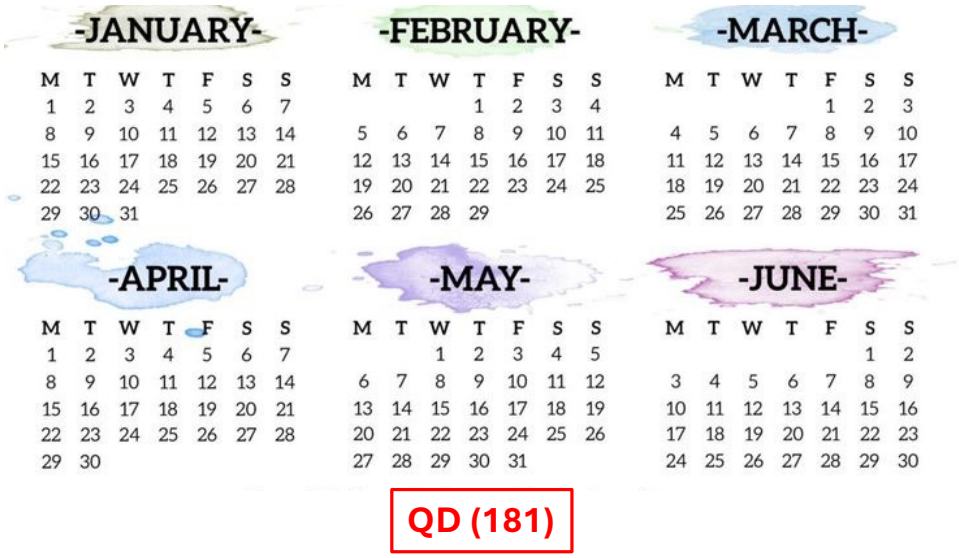
3 4 5 6 7 8 9
10 11 12 13 14 15 16
17 18 19 20 21 22 23
24 25 26 27 28 29 30

QD (181)


-JANUARY-
M T W T F S S
1
8
15
22
29
-FEBRUARY-
M T W T F S S
5
12
19
26
-MARCH-
M T W T F S S
4
11
18
25
-APRIL-
M T W T F S S
1
8
15
22
29
-MAY-
M T W T F S S
6
13
20
27
-JUNE-
M T W T F S S
3
10
17
24

QW (26)



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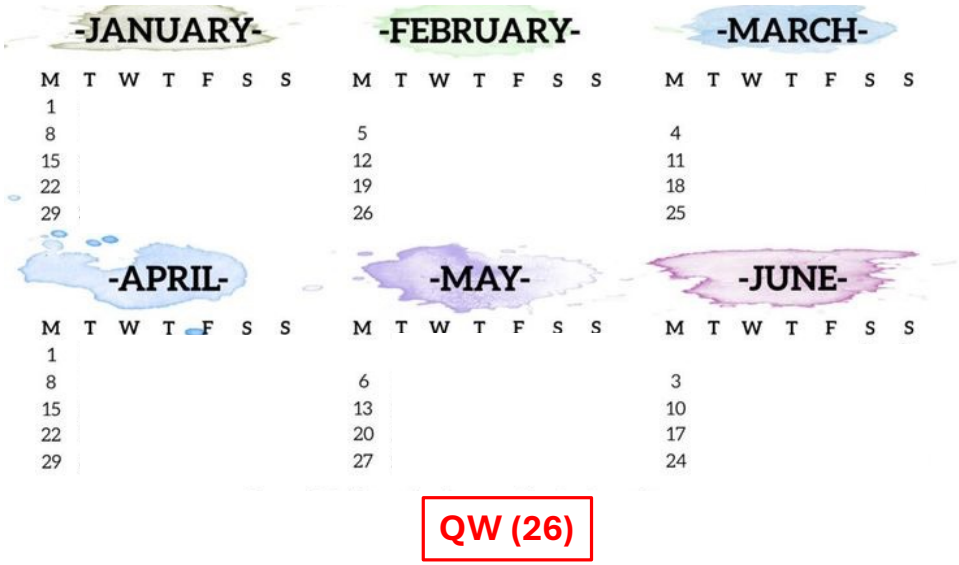

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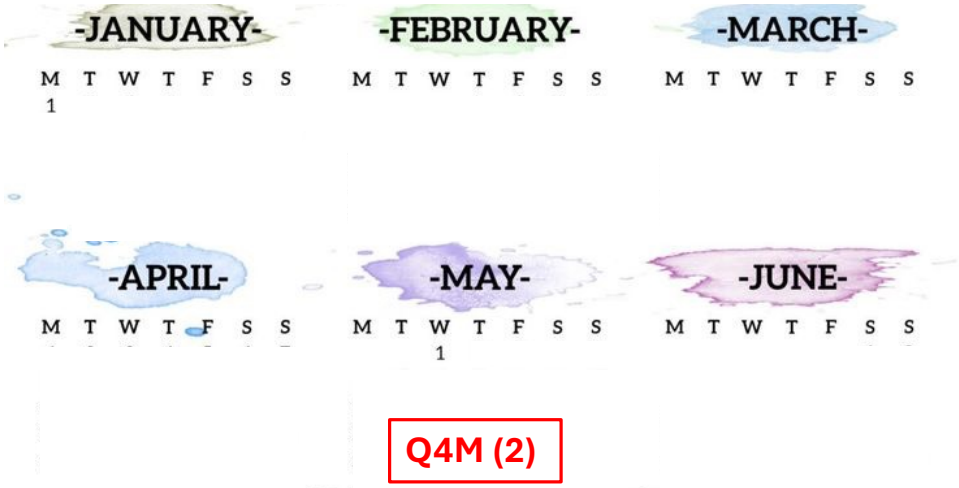
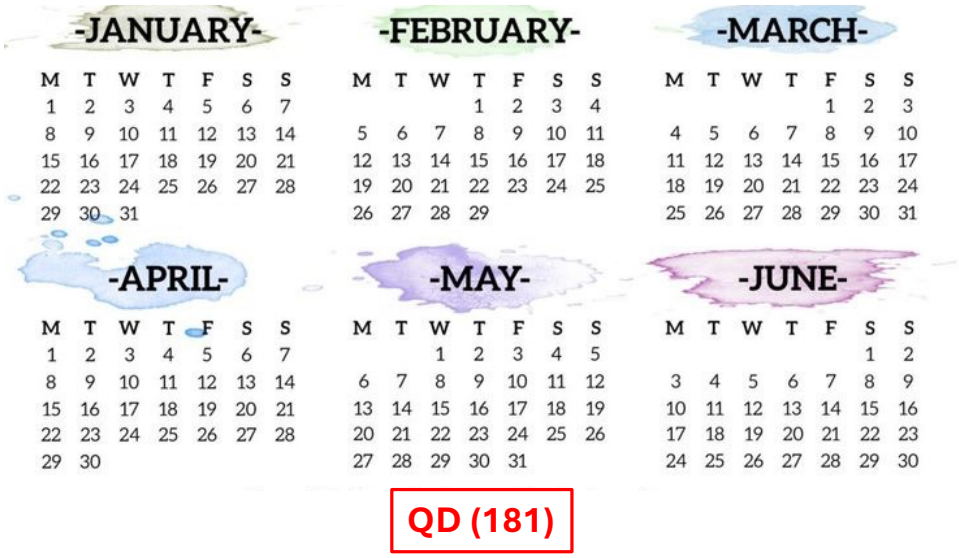


Q4M (2)



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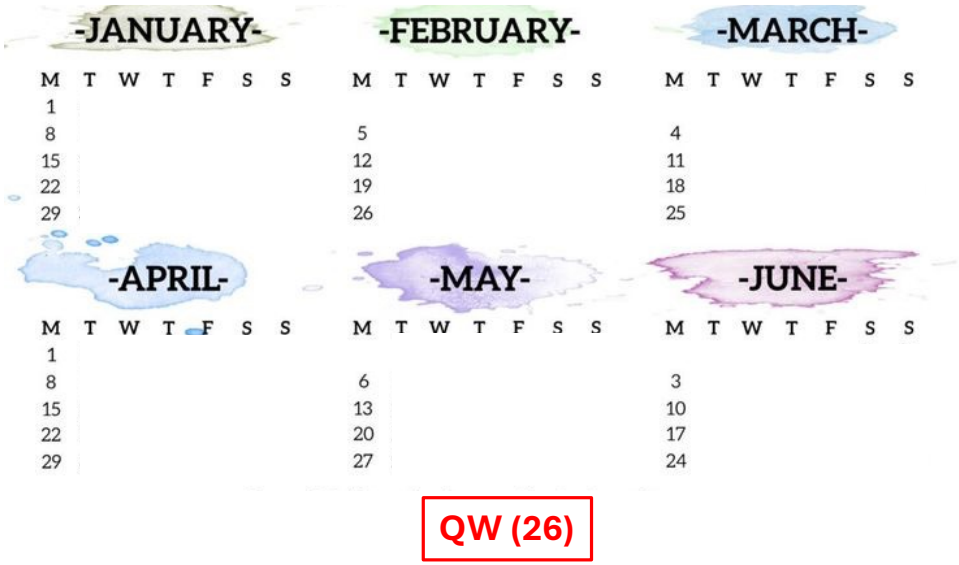

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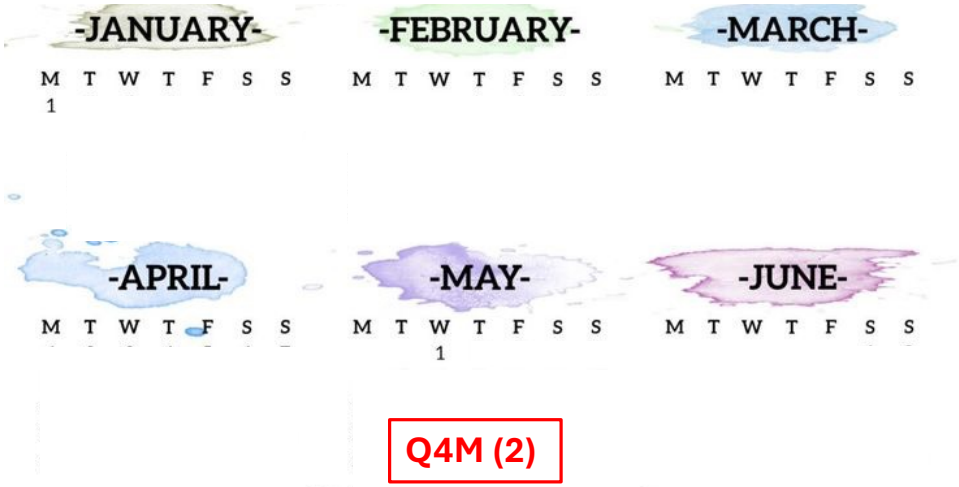
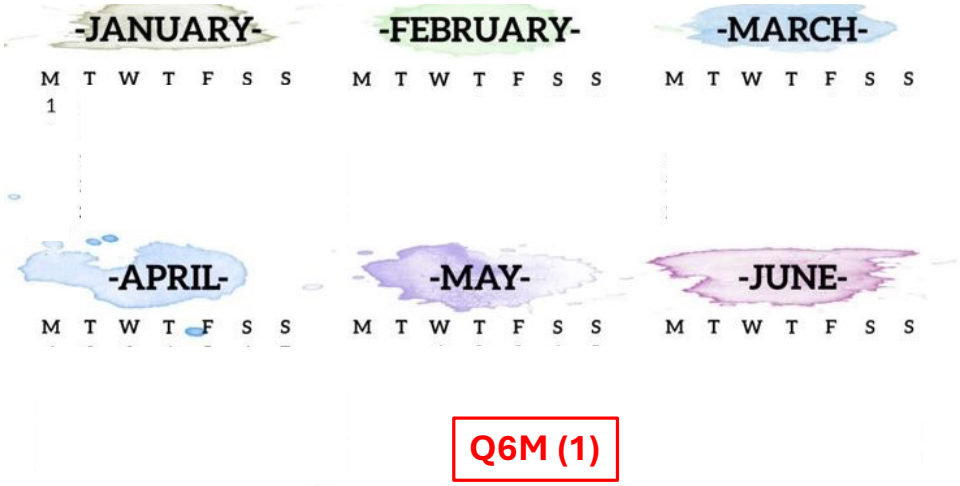
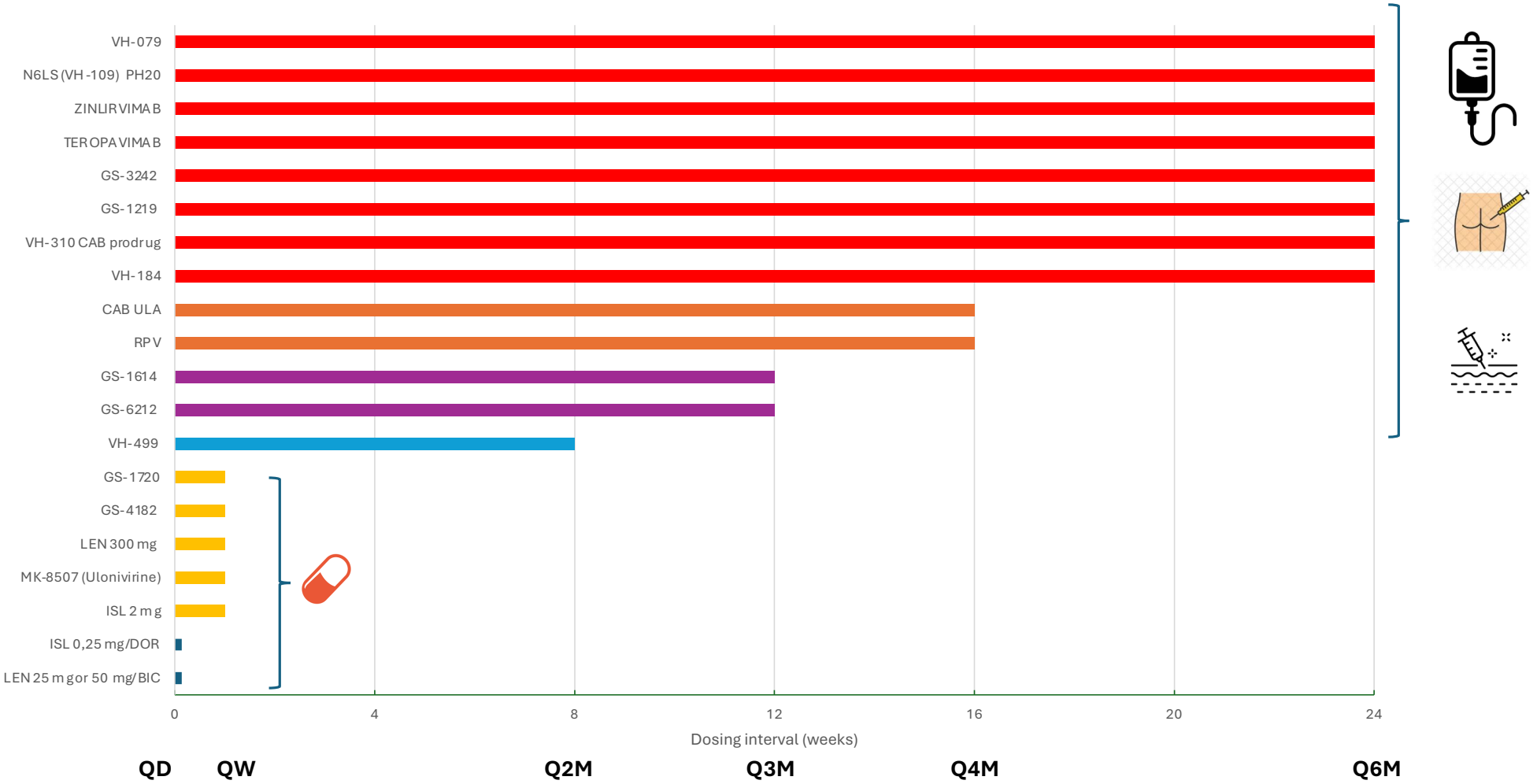


Q4M (2)



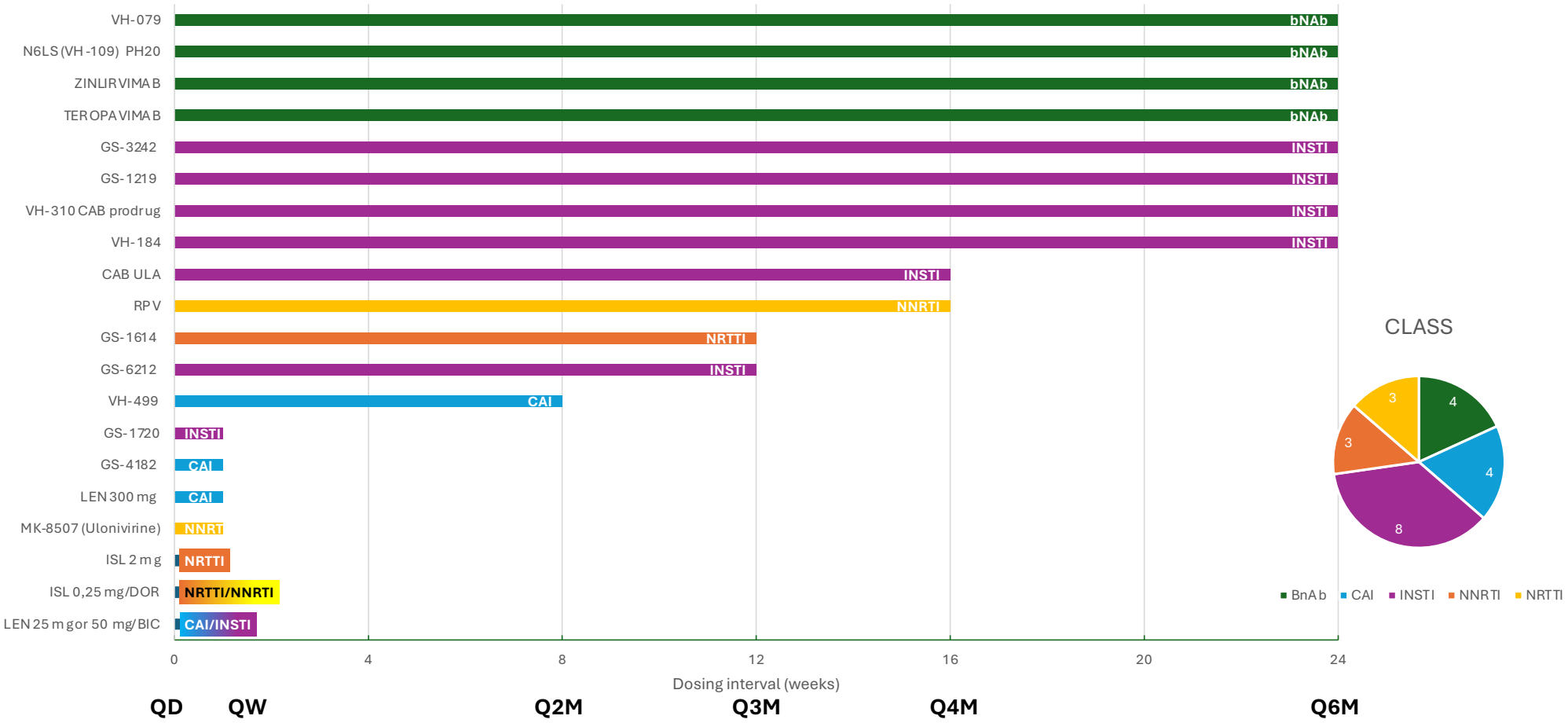
Q6M (1)

ROUTE

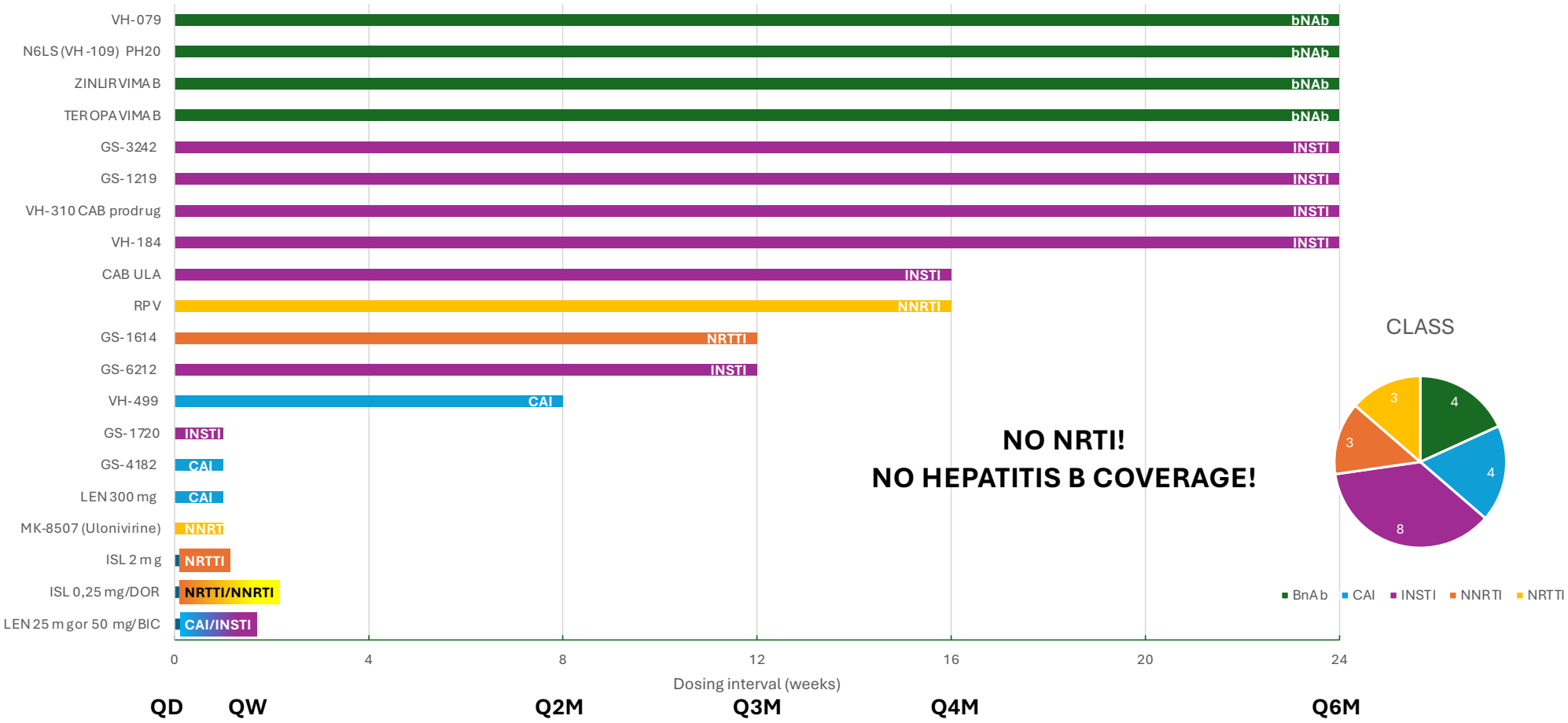


*For a number of drugs the interval is aspirational, still under investigation

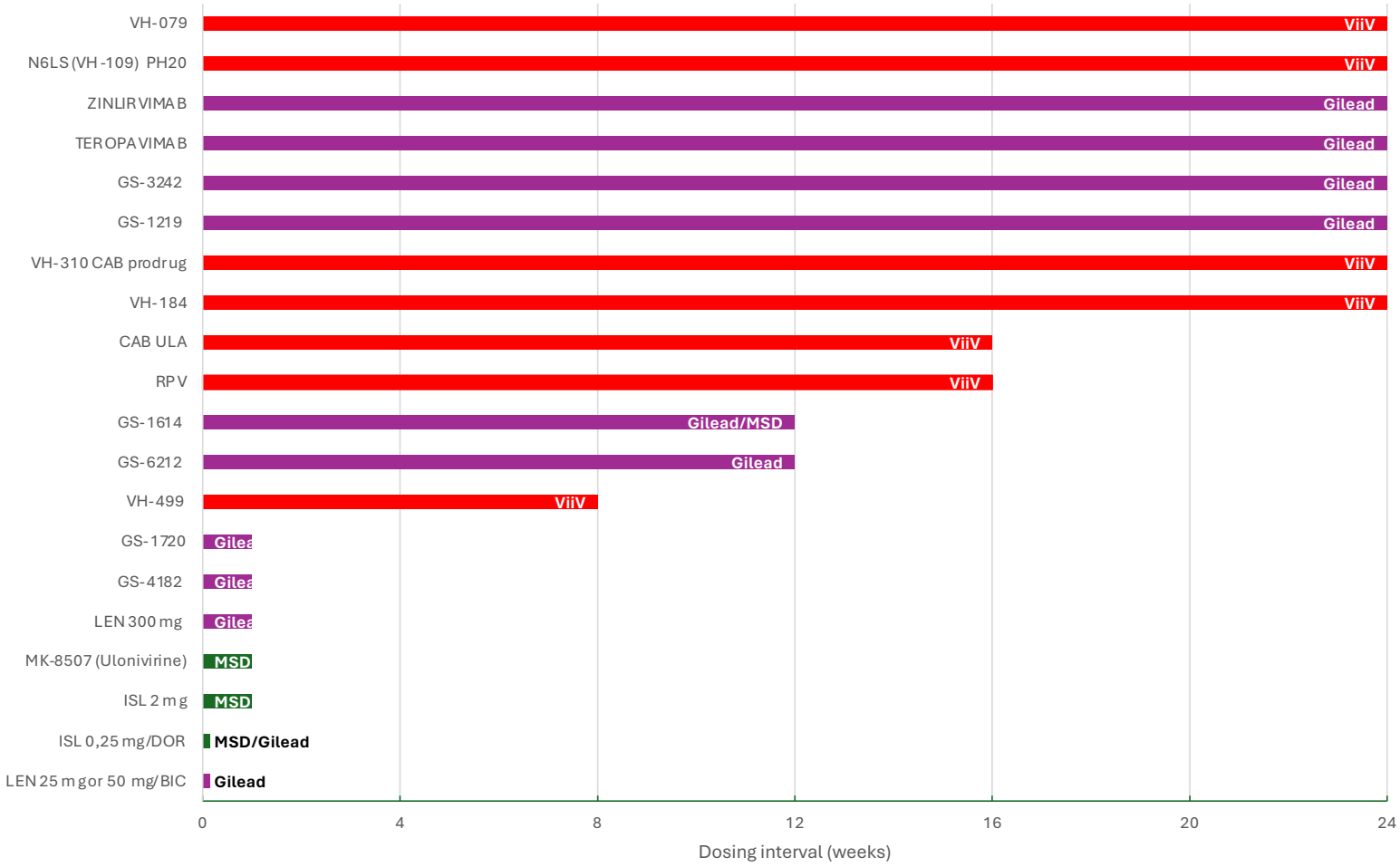
CLASS


VH-079
N6LS (VH-109) PH20
ZINLIRVIMAB
TEROPAVIMAB
GS-3242
GS-1219
VH-310 CAB prodrug
VH-184
CAB ULA
RPV
GS-1614
GS-6212
VH-499
GS-1720
GS-4182
LEN 300 mg
MK-8507 (Ulonivirine)
ISL 2 mg
ISL 0,25 mg/DOR
LEN 25 mg or 50 mg/BIC
bNAb
INSTI
NNRTI
NRTTI
CAI
CAI/INSTI
NRTTI/NNRTI
0
4
8
12
16
20
24
Dosing interval (weeks)
QD
QW
Q2M
Q3M
Q4M
Q6M
CLASS
4
4
8
3
3
BnAb
CAI
INSTI
NNRTI
NRTTI

CLASS

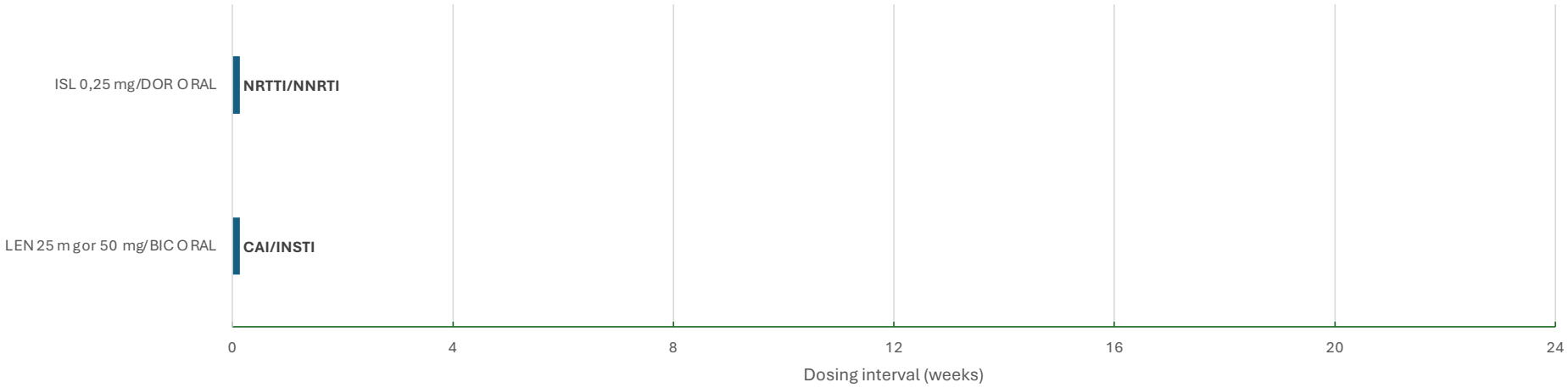

VH-079
N6LS (VH-109) PH20
ZINLIRVIMAB
TEROPAVIMAB
GS-3242
GS-1219
VH-310 CAB prodrug
VH-184
CAB ULA
RPV
GS-1614
GS-6212
VH-499
GS-1720
GS-4182
LEN 300 mg
MK-8507 (Ulonivirine)
ISL 2 mg
ISL 0,25 mg/DOR
LEN 25 mg or 50 mg/BIC
bNAb
INSTI
NNRTI
NRTTI
CAI
NRTTI/NNRTI
CAI/INSTI
0
4
8
12
16
20
24
Dosing interval (weeks)
QD
QW
Q2M
Q3M
Q4M
Q6M
NO NRTI!
NO HEPATITIS B COVERAGE!
CLASS
4
4
8
3
3
BnAb
CAI
INSTI
NNRTI
NRTTI

COMPANY

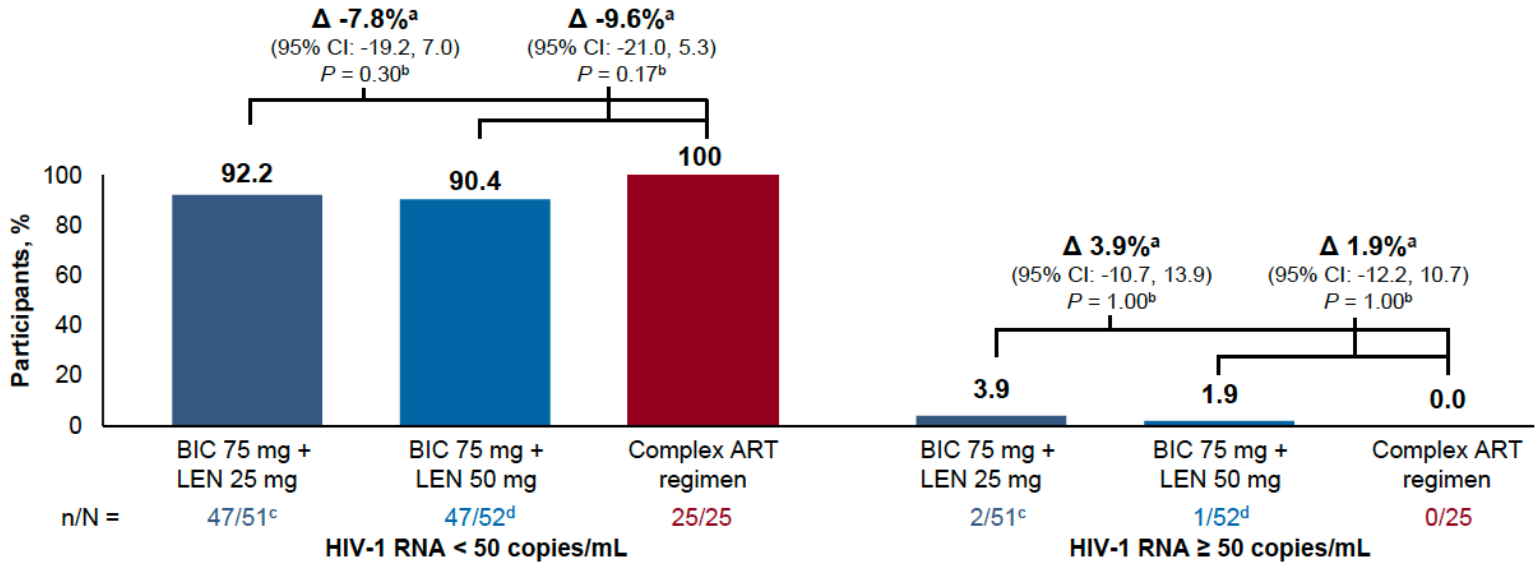

VH-079
N6LS (VH-109) PH20
ZINLIRVIMAB
TEROPAVIMAB
GS-3242
GS-1219
VH-310 CAB prodrug
VH-184
CAB ULA
RPV
GS-1614
GS-6212
VH-499
GS-1720
GS-4182
LEN 300 mg
MK-8507 (Ulonivirine)
ISL 2 mg
ISL 0,25 mg/DOR
LEN 25 mg or 50 mg/BIC
ViiV
Gilead
Gilead/MSD
MSD
MSD/Gilead
0
4
8
12
16
20
24
Dosing interval (weeks)

QD

QD


ISL 0,25 mg/DOR ORAL
NRTTI/NNRTI
LEN 25 mg or 50 mg/BIC ORAL
CAI/INSTI
0
4
8
12
16
20
24
Dosing interval (weeks)

Virologic Suppression at Week 48 (US FDA Snapshot Analysis)



[a]Difference in % (95% CI): BIC + LEN - complex ART regimen calculated based on an unconditional exact method using two inverted one-sided tests. [b]Based on Fisher exact test.
[c]Two participants had no virologic data in the Week 48 window as they discontinued study drug before Week 48 visit; one participant due to AE and one participant due to participant decision
[d]Four participants had no virologic data in the Week 48 window as they discontinued study drug before Week 48 visit due to AE, death, participant decision, and investigator decision (n = 1 for each).

- Rates of virologic suppression were high across all treatment groups at Week 48
- Changes in CD4 cell count and percentage were comparable among groups

- A BIC 75 mg/LEN 50 mg STR will be assessed in the Phase 3 part of this study; additional data from Phase 2 and Phase 3 will be presented at future congresses

Mounzer. AIDS 2024. Abstr OAB2602.

ARTISTRY-2 (GS-US-621-6290): Phase 3, randomized, double-blind study (U.S.)[1]

ARTISTRY 2 ‡

BIC/LEN in PWH Switching From B/F/TAF: Study Design

GO BACK

N=546[1]

Randomized, double-blind, multicenter study[1]

Outcomes: Safety and efficacy of BIC/LEN FDC in virologically suppressed PWH[1]

March 2024 – ongoing[1]

Adults with VS for 6 months[1]

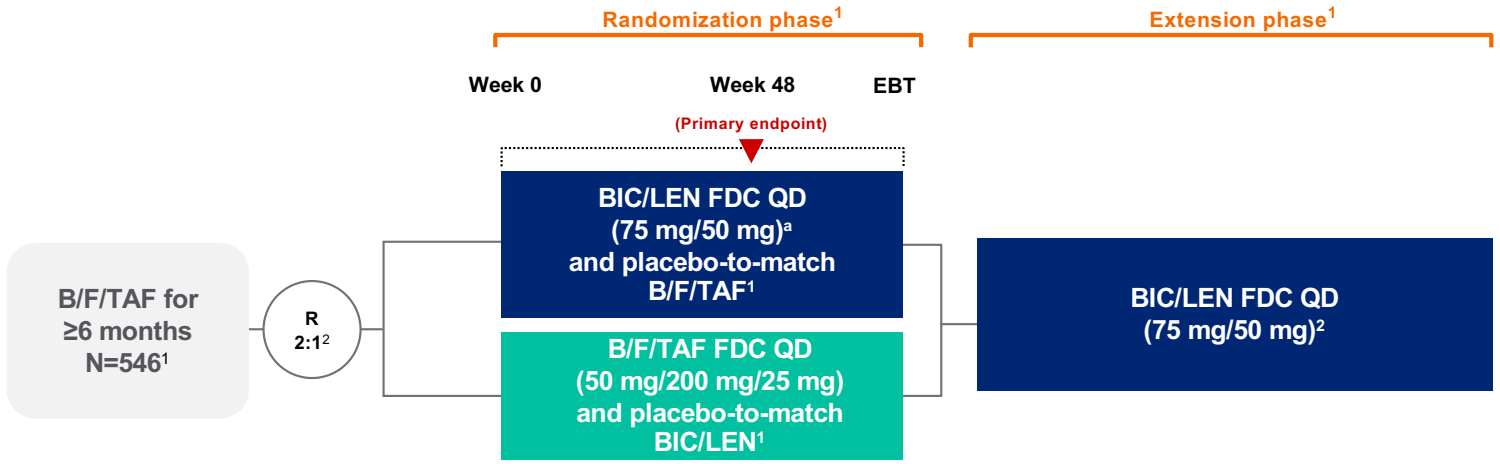
VL <50 c/mL[1]

On B/F/TAF[1]

No history of exposure to LEN or resistance to BIC or TAF[1]

No history of chronic HBV infection[1]

eGFR ≥30 mL/min[1]



Primary Outcome:[1] **Proportion of participants with HIV-1 RNA ≥50 c/mL at Week 48 (FDA Snapshot)**

Secondary Outcomes:[1] Proportion of participants with HIV-1 RNA <50 c/mL at Weeks 48 and 96, and with ≥50 c/mL at Week 96 (FDA Snapshot)
Change from baseline in CD4 Count at Weeks 48 and 96
AEs through Weeks 48 and 96

[a]Participants will receive a 2-day oral loading dose of LEN 600 mg on Day 1 and on Day 2 in addition to BIC/LEN FDC
EBT, end of blinded treatment; STR, single tablet regimen; VL, viral load; VS, virologic suppression
1. NCT06333808. https://clinicaltrials.gov/study/NCT06333808 (accessed May 21, 2024); 2. Data on file. Gilead Sciences, Inc.

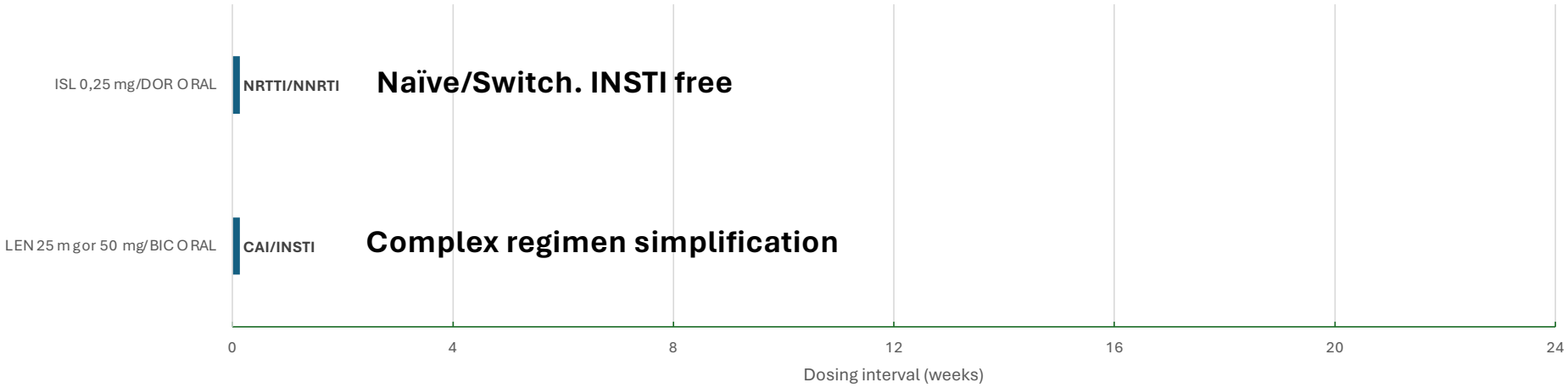
DOR/ISL (100 mg/0.25 mg)
Phase 3 Studies for HIV-1 Treatment

Study*	Study Intervention	Design	Population	Sample Size
051[1]	**DOR/ISL (100 mg/0.25 mg) QD** compared with ***baseline ART***	Open-label; 2:1 randomization	Virologically Suppressed	N=501
052[2]	**DOR/ISL (100 mg/0.25 mg) QD** compared with ***BIC/FTC/TAF***	Blinded; 2:1 randomization	Virologically Suppressed	N=501
053[3]	**DOR/ISL (100 mg/0.25 mg) QD** compared with ***BIC/FTC/TAF***	Blinded; 1:1 randomization	ART-naive	N=500
054[4]	**DOR/ISL (100 mg/0.25 mg) QD**	Open-label, single arm, de-escalation from **DOR/ISL (100 mg/0.75 mg)**	Virologically Suppressed	N~650

* Study numbers are hyperlinks to CinicalTrials.gov
DOR: doravirine; ISL: islatravir; ART: antiretroviral therapy; BIC: bictegravir; FTC: emtricitabine; TAF: tenofovir alafenamide

1. Study 051 ClinicalTrials.gov. Accessed 1/25/2024
2. Study 052 ClinicalTrials.gov. Accessed 1/25/2024
3. Study 053 ClinicalTrials.gov. Accessed 1/25/2024
4. Study 054 ClinicalTrials.gov. Accessed 1/25/2024

QD


ISL 0,25 mg/DOR ORAL
NRTTI/NNRTI
Naïve/Switch. INSTI free
LEN 25 mg or 50 mg/BIC ORAL
CAI/INSTI
Complex regimen simplification
0
4
8
12
16
20
24
Dosing interval (weeks)

QW

2018

Table 1. Distribution and Correlates of Interest in Switching to Novel ART Regimens (n = 263)

		1 Pill Once a Week	2 Shots Every Other Month	2 Implants Every 6 Months
Interest in switching, No. (%)				
Not at all interested		38 (14)	100 (38)	152 (58)
Somewhat interested		52 (20)	60 (23)	61 (23)
Very interested		173 (66)	101 (39)	5 (18)
No.		263	261	261
		β (SE)	β (SE)	β (SE)
Clinic, Duke vs South Carolina, No. (%)	132 (50.2)	0.02 (0.20)	0.22 (0.23)	0.22 (0.22)
Age, mean (SD), years	46.7 (11.8)	–0.01 (0.01)	–0.02* (0.01)	–0.01 (0.01)
Gender, male vs female, No. (%)	148 (56.3)	–0.33 (0.20)	–0.12 (0.24)	0.10 (0.22)
More than high school education, yes vs no, No., (%)	109 (41.4)	0.43* (0.21)	1.04*** (0.24)	0.72** (0.23)
Race, white vs minority, No. (%)	51 (19.4)	–0.04 (0.25)	0.16 (0.30)	–0.24 (0.28)
Time on ART, mean (SD), years	12.1 (8.3)	–0.02 (0.01)	–0.03 (0.02)	–0.01 (0.01)
AIDS diagnosis, ever vs never, No. (%)	41 (15.6)	0.32 (0.25)	0.27 (0.30)	–0.12 (0.28)
Viral load <200, self-reported, yes vs no, No. (%)	215 (81.7)	0.28 (0.24)	–0.23 (0.29)	0.27 (0.27)
Missed dose, past 2 weeks, any vs none, No. (%)	58 (22.1)	–0.09 (0.23)	–0.15 (0.27)	0.00 (0.25)
Current side effects, any vs none, No. (%)	90 (34.2)	0.26 (0.20)	0.22 (0.23)	0.10 (0.22)
Long-term effects, any vs none, No. (%)	103 (39.2)	0.34 (0.20)	0.56* (0.24)	0.21 (0.22)
Single-tablet regimen, yes vs no, No. (%)	155 (58.9)	–0.44* (0.20)	–0.15 (0.23)	–0.44* (0.22)
Food restriction, any vs none, No. (%)	148 (56.3)	0.04 (0.19)	0.27 (0.23)	0.15 (0.21)
No.	263	247	247	247

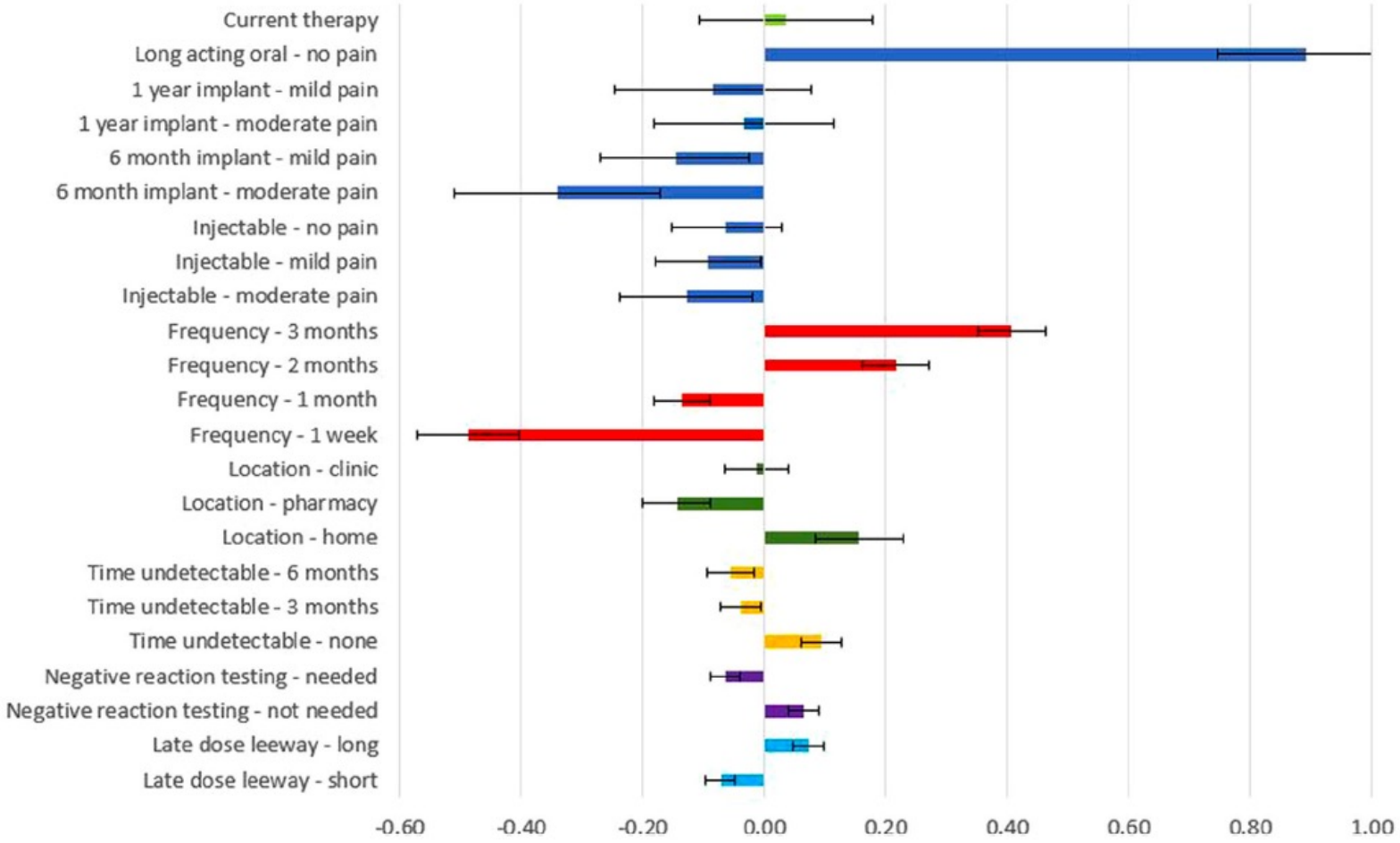
Results from a multivariate linear regression model. Dependent variables range from 1–5. Positive values for β indicate greater interest in switching. *, **, and *** denote statistical significance at the 0.05, 0.01, and 0.001 levels, respectively. Sixteen observations were excluded from the multivariate model due to missing data on 1 or more outcome variables (n = 3) or covariates (n = 13).

Abbreviation: ART, antiretroviral therapy; No., number of patients; SD, standard deviation; SE, standard error.

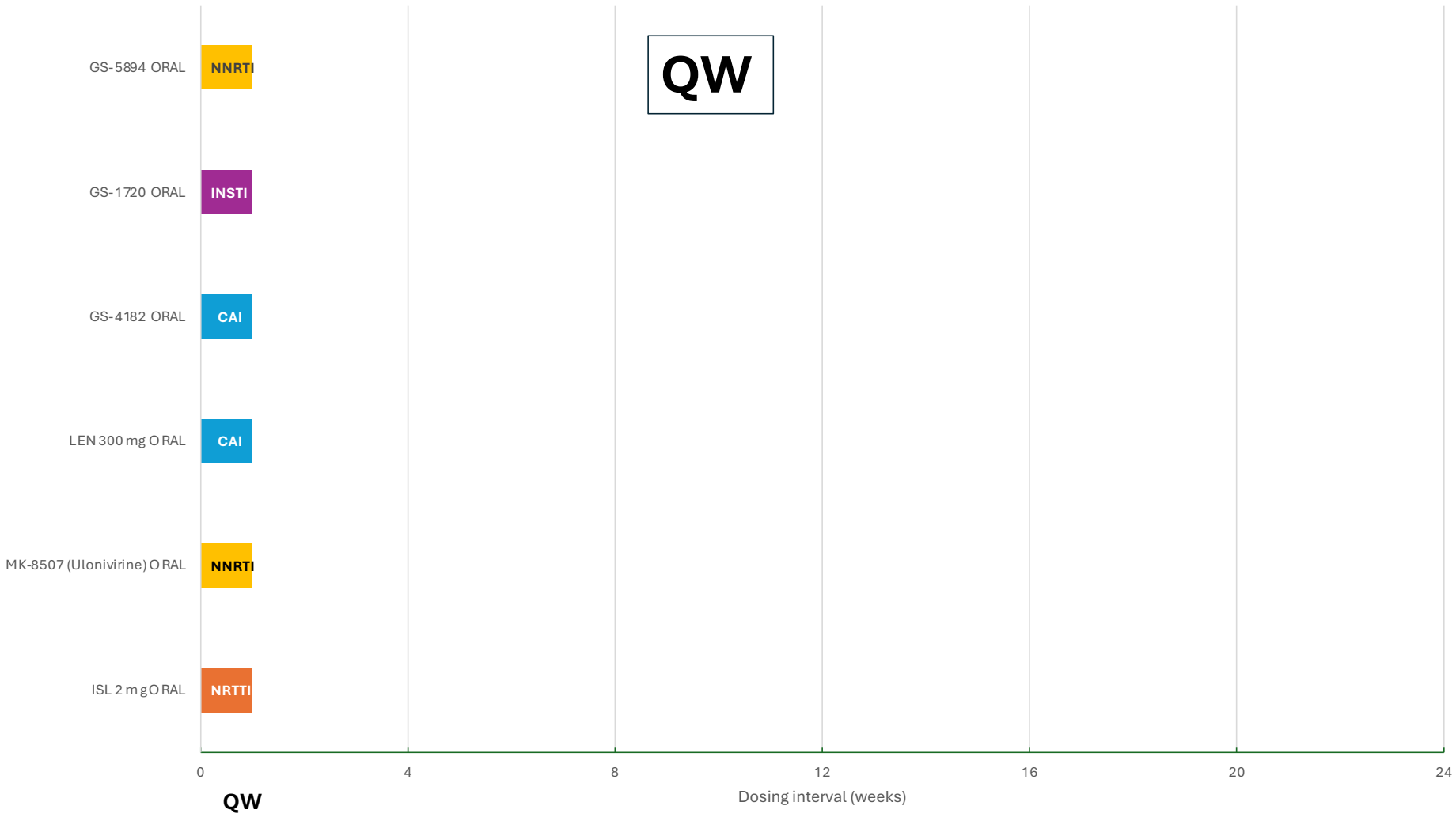
OFID 2018; DOI: 10.1093/ofid/ofy247

2023

n = 700



Graham SM et al. Journal of the International AIDS Society 2023, 26(S2):e26099

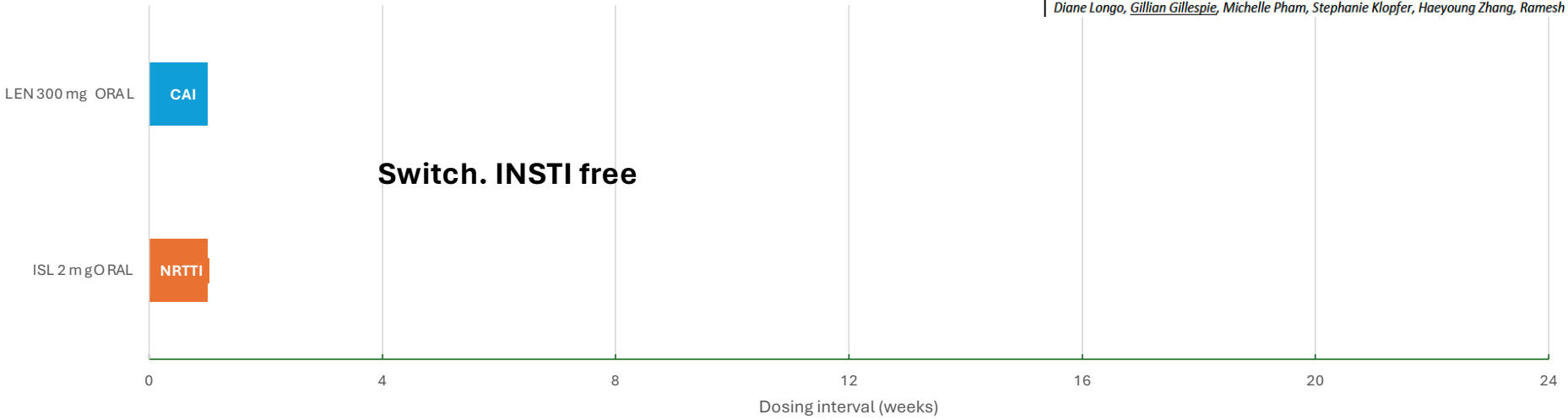

QW
GS-5894 ORAL
NNRTI
GS-1720 ORAL
INSTI
GS-4182 ORAL
CAI
LEN 300 mg ORAL
CAI
MK-8507 (Ulonivirine) ORAL
NNRTI
ISL 2 mg ORAL
NRTTI
0
4
8
12
16
20
24
Dosing interval (weeks)
QW

QW

HIV DRUG THERAPY GLASGOW 2024

O21: Once-weekly islatravir plus lenacapavir in virologically suppressed PWH: week 48 safety, efficacy, and metabolic changes
Amy E Colson, *Community Resource Initiative, Boston, MA, USA*

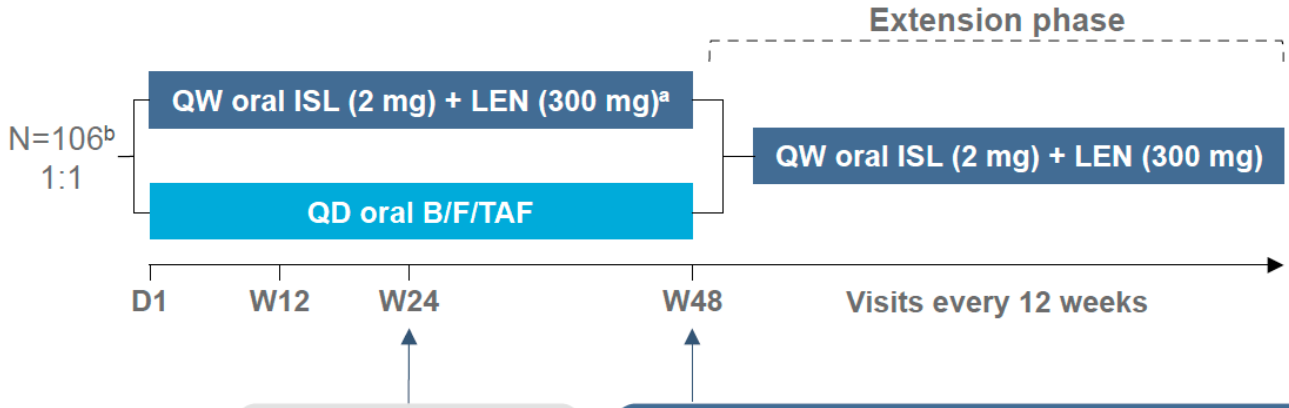
P224 **Pharmacokinetics of oral islatravir (ISL) plus lenacapavir (LEN) given once weekly in an open-label, active-controlled, phase II study of virologically suppressed people with HIV-1**
Diane Longo, Gillian Gillespie, Michelle Pham, Stephanie Klopfer, Haeyoung Zhang, Ramesh Palaparthy,



Methods

A Phase 2, Open-label, Active-controlled Study in Virologically Suppressed PWH

Eligibility criteria
- Aged ≥18 years
- On B/F/TAF for >6 months
- HIV-1 RNA <50 c/mL for >6 months
- No history of virologic failure
- CD4+ T-cell count ≥350 cells/µl
- Lymphocyte count ≥900 cells/µl
- No HBV infection

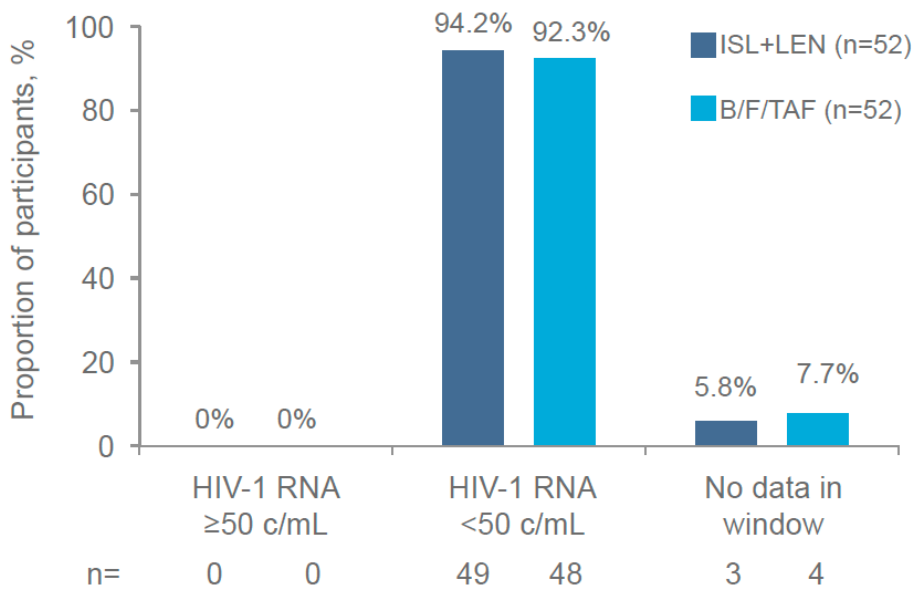


Primary endpoint:[1]
- Proportion with HIV-1 RNA ≥50 c/mL at Week 24 per FDA Snapshot algorithm

Secondary endpoints included in this presentation:
- Proportion with HIV-1 RNA ≥50 c/mL at Week 48
- Proportion with HIV-1 RNA <50 c/mL at Week 48
- Change from baseline in CD4+ T-cell count
- AEs leading to study drug discontinuation

[a]600 mg of LEN was given on D1 and D2 for pharmacologic loading. [b]Randomized, N=106; dosed, N=104.
AE, adverse events; **B/F/TAF**, bictegravir/emtricitabine/tenofovir alafenamide; **c/mL**, copies/mL; **D**, day; **FDA**, Food and Drug Administration; **HBV**, hepatitis B virus; **ISL**, islatravir; **LEN**, lenacapavir; **PWH**, people with HIV-1; **QD**, daily; **QW**, weekly; **W**, week.
1. Colson A, et al. CROI 2024; Abstract 208.

Virologic Outcomes at Week 48 by FDA Snapshot Algorithm



Participants with no data in window:

ISL+LEN

- Two participants discontinued due to AEs not related to study drug
- One participant discontinued due to other reasons not related to study drug
- All participants had HIV-1 RNA <50 c/mL at study discontinuation

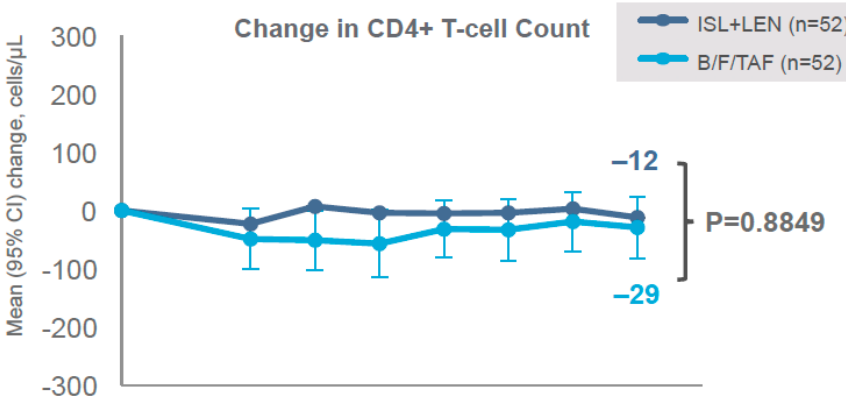
B/F/TAF

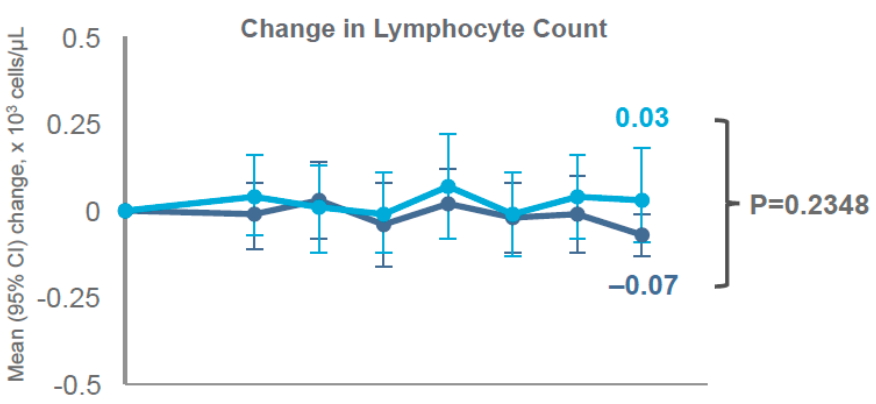
- Three participants discontinued due to other reasons not related to study drug and had HIV-1 RNA <50 c/mL at study discontinuation
- One participant had missing data during window, but remained on study drug

Participants in both treatment groups maintained high rates of virologic suppression

AE, adverse event; **B/F/TAF**, bictegravir/emtricitabine/tenofovir alafenamide; **c/mL**, copies/mL; **FDA**, Food and Drug Administration; **ISL**, islatravir; **LEN**, lenacapavir.

CD4+ T-cell and Lymphocyte Count Changes Through Week 48





Mean Values	BL	W12	W18	W24	W30	W36	W42	W48
ISL+LEN	755	732	766	755	754	756	761	746
B/F/TAF	818	758	767	761	785	783	797	787

Mean Values	BL	W12	W18	W24	W30	W36	W42	W48
ISL+LEN	1.94	1.94	1.98	1.92	1.96	1.94	1.93	1.88
B/F/TAF	1.95	1.99	1.97	1.96	2.03	1.96	2.00	1.99

- There were no significant differences between groups in mean change from baseline in CD4+ T-cell or lymphocyte counts at Week 48
- No participants discontinued due to a decrease in CD4+ T-cell or lymphocyte counts

B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; **BL**, baseline; **ISL**, islatravir; **LEN**, lenacapavir; **W**, Week.

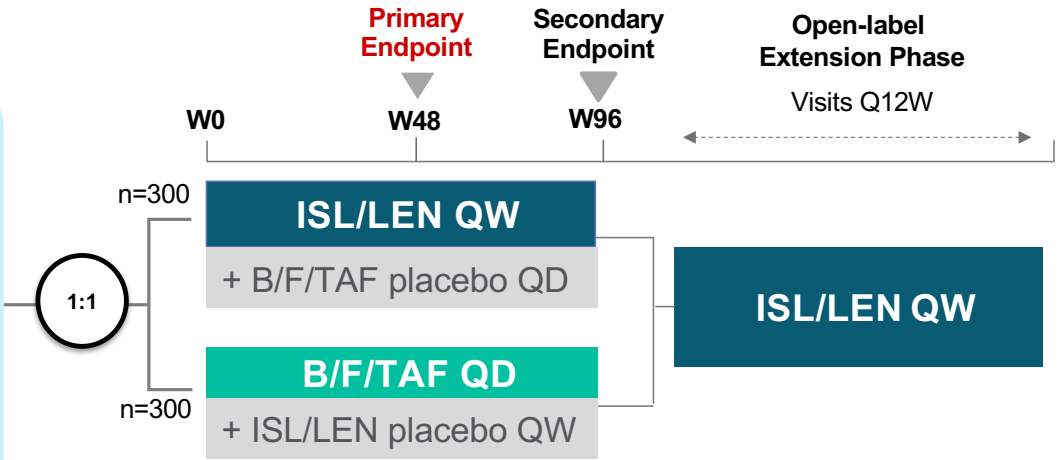
ISL/LEN Long-Acting Oral Weekly in VS PWH

ISLEND-1

Phase 3, Randomized, Double-blind, Active-control, Multicenter Study to Evaluate Efficacy, Safety, and PK of ISL/LEN in VS PWH (N=600)[1,2]

Key Inclusion Criteria

- VS PWH
- ≥18 years old
- On B/F/TAF for ≥24 weeks
- HIV-1 RNA <50 c/mL for ≥24 weeks
- No prior VF



Primary Endpoints:

- % with HIV-1 RNA ≥50 c/mL at W48

Secondary Endpoints:

- % with HIV-1 RNA ≥50 c/mL at W96
- % with HIV-1 RNA <50 c/mL at W48 and W96
- Change from BL CD4 cell count at W48 and W96
- % discontinuation of ISL/LEN due to TEAEs
- PK and PROs[a]

[a]PROs are an exploratory endpoint

BL, baseline; PK, pharmacokinetics; PRO, participant-reported outcome; QD, every day; QW, every week; Q12W, every 12 weeks; TEAEs, treatment-emergent adverse events; VF, virologic failure; VS, virologically suppressed; W, week

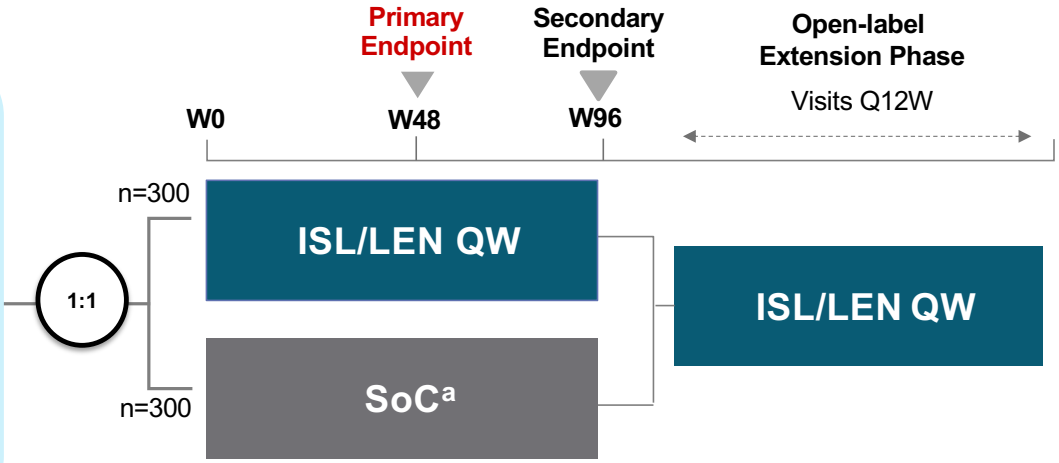
1. NCT06630286. https://clinicaltrials.gov/study/NCT06630286 (accessed October 08, 2024); 2. Data on file

ISL/LEN Long-Acting Oral Weekly in VS PWH

Phase 3, Randomized, Open-Label, Active-control, Multicenter Study to Evaluate Efficacy, Safety, and PK of ISL/LEN in VS PWH (N=600)[1,2]

Key Inclusion Criteria

- VS PWH
- ≥18 years old
- SoC[a] oral treatment for ≥24 weeks
- HIV-1 RNA <50 c/mL for ≥24 weeks
- No prior VF



Primary Endpoints:

- % with HIV-1 RNA ≥50 c/mL at W48

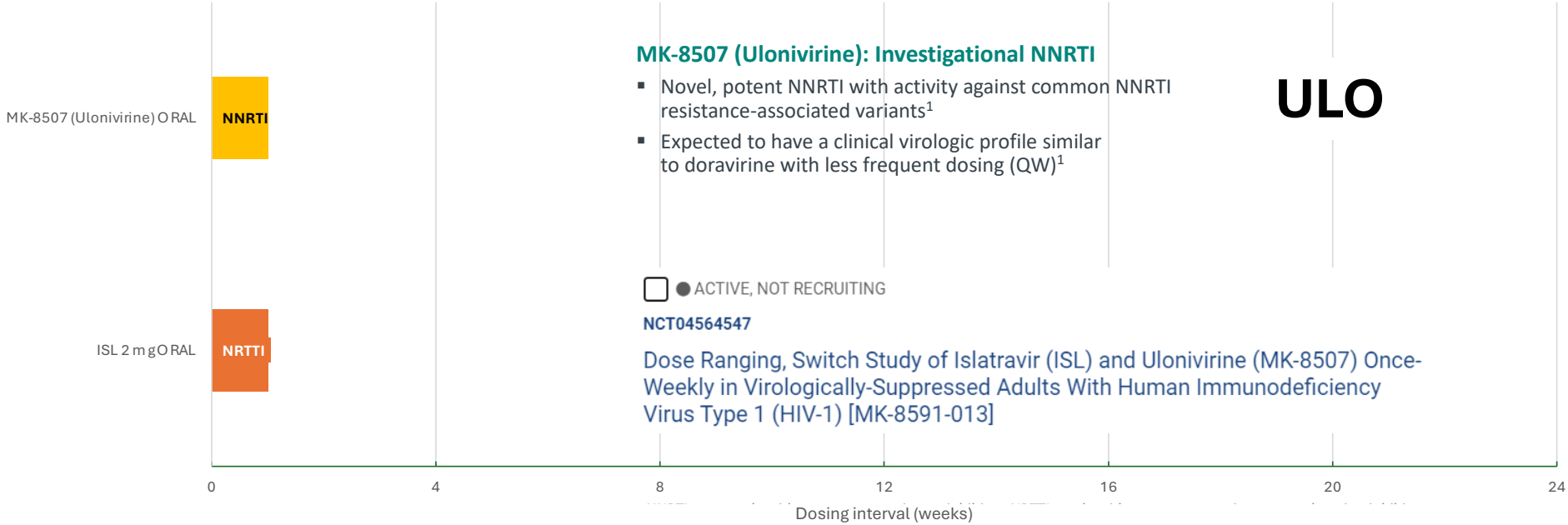
Secondary Endpoints:

- % with HIV-1 RNA ≥50 c/mL at W96
- % with HIV-1 RNA <50 c/mL at W48 and W96
- Change from BL CD4 cell count at W48 and W96
- % discontinuation of ISL/LEN due to TEAEs
- PK and PROs[b]

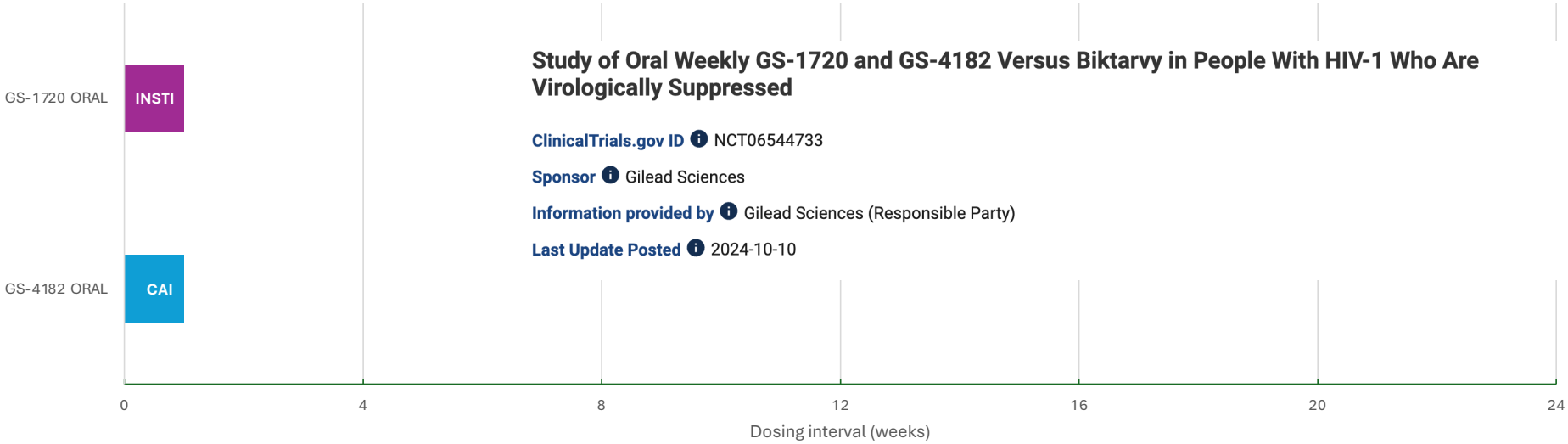
[a]SoC oral regimen: INSTI + 1 or 2 NRTIs, boosted PI + 2 NRTIs, or NNRTI + 2 NRTIs [b]PROs are an exploratory endpoint
BL, baseline; PK, pharmacokinetics; PRO, participant-reported outcome; QW, every week; Q12W, every 12 weeks; SoC, standard of care; TEAEs, treatment-emergent adverse events; VF, virologic failure; VS, virologically suppressed; W, week

1. NCT06630299. https://clinicaltrials.gov/study/NCT06630299 (accessed October 08, 2024); 2. Data on file

QW


MK-8507 (Ulonivirine) ORAL
NNRTI
ISL 2 mg ORAL
NRTTI
MK-8507 (Ulonivirine): Investigational NNRTI
Novel, potent NNRTI with activity against common NNRTI resistance-associated variants[1]
Expected to have a clinical virologic profile similar to doravirine with less frequent dosing (QW)[1]
ULO
ACTIVE, NOT RECRUITING
NCT04564547
Dose Ranging, Switch Study of Islatravir (ISL) and Ulonivirine (MK-8507) Once-Weekly in Virologically-Suppressed Adults With Human Immunodeficiency Virus Type 1 (HIV-1) [MK-8591-013]
0
4
8
12
16
20
24
Dosing interval (weeks)

QW



Study of Oral Weekly GS-1720 and GS-4182 Versus Biktarvy in People With HIV-1 Who Are Virologically Suppressed

ClinicalTrials.gov ID NCT06544733

Sponsor Gilead Sciences

Information provided by Gilead Sciences (Responsible Party)

Last Update Posted 2024-10-10

HIV DRUG THERAPY GLASGOW 2024

P036 **Effect of acid reducing agents on the pharmacokinetics of oral GS-4182**

Naveed Shaik, Sean Regan, Deqing Xiao, Furong Wang, Jason Hindman,

Treatment Pipeline Data Presented at AIDS 2024: GS-1720 and GS-4182

	GS-1720 A novel, oral weekly INSTI[1,2]	GS-4182 A novel, oral weekly LEN prodrug[3,4]
Dosing	Once per week	Once per week
Profile	• Potent INSTI (IC_{50} = 6.2 ± 0.4 nM) • Potential high *in vitro* barrier to resistance similar to BIC[5] • Activity against common INSTI-R site-directed HIV-1 mutants[a] • Median $t_{1/2}$: 9.3 days	• Novel, solubilizing prodrug with greater intestinal LEN absorption and improved systemic exposure in comparison with oral LEN • Smaller tablet size may reduce pill burden • Median LEN $t_{1/2}$ ~11 days
Safety	Favorable safety profile and well tolerated at doses up to 1350 mg in Phase 1	Well tolerated with a favorable safety profile at doses of 200 or 400 mg QW in Phase 1

GS-1720 and GS-4182 are being developed as a first-in-class QW oral INSTI + capsid inhibitor combination for HIV treatment, moving into Phase 2

Click for study info

[a]Mean EC_{50} fold change relative to wild type was 2.7 for E92Q, 2.5 for Y143R, 1.0 for Q148R, 1.9 for N155H, 2.0 for R263K, 1.8 for E92Q/N155H, 9.5 for E138K/Q148K and 5.5 for G140S/Q148R

EC_{50}, effective concentration of half maximal response; QW, once weekly. 1. Hansen D, et al. AIDS 2024, Abstract and Poster THPEA025; 2. Zhang H, et al. AIDS 2024, Poster WEPEB116; 3. Subramanian R, et al. AIDS 2024, Abstract and Poster WEPEA031; 4. Shaik N, et al. AIDS 2024, Poster WEPEB117; 5. Data on file. Gilead Sciences, Inc.

WONDERS 1 (GS-US-695-6509): Phase 2/3 randomized study

Oral Weekly GS-1720 + GS-4182 in Virologically Suppressed PWH[1]

Phase 2 Study Design *(Data presented on this slide were not part of the AIDS 2024 program)*

GS-1720, a novel and potent INSTI, and GS-4182, a novel oral QW LEN prodrug, are being developed as a first-in-class QW oral INSTI + capsid inhibitor combination for HIV treatment

N=75

VS PWH on B/F/TAF

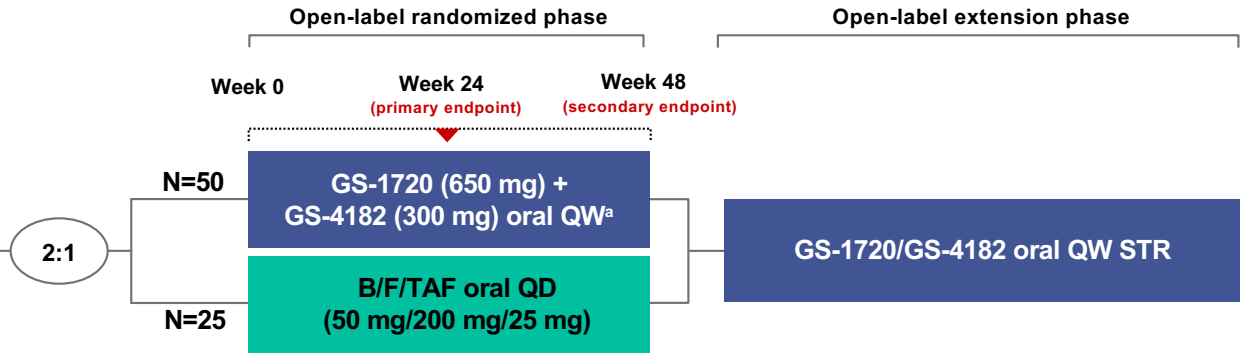
Outcomes

Primary: HIV-1 RNA ≥50 c/mL at Week 24 (FDA Snapshot)

Secondary: HIV-1 RNA ≥50 c/mL at Week 12 and Week 48 (FDA Snapshot)

Estimated Start: September 2024

- Adults ≥18 years old
- HIV-1 RNA <50 c/mL for ≥24 weeks
- B/F/TAF use for ≥24 weeks
- CD4 count ≥200 cells/mm^3
- No history of exposure to LEN, GS-1720 or GS-4182
- No documented INSTI resistance or failure
- No active or history of chronic HBV infection
- eGFR ≥60 mL/min



Countries participating in Phase 2: Canada, Puerto Rico, United States[2]

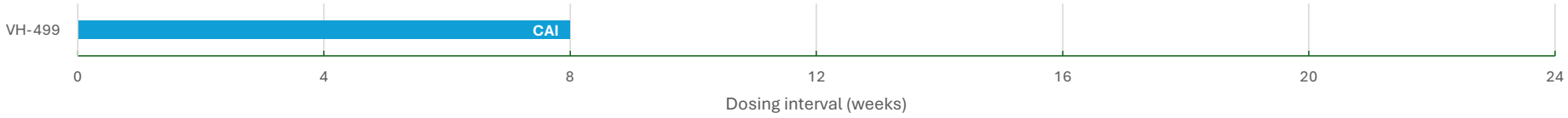
[a]Participants will receive a 1-day oral loading dose of GS-1720 (1300 mg) and GS-4182 (600 mg) on Day 1

QW, once weekly; STR, single tablet regimen; VS, virologically suppressed

1. NCT06544733. https://clinicaltrials.gov/study/NCT06544733 (accessed August 12, 2024); 2. Data on file. Gilead Sciences, Inc.

Q2M

Q2M

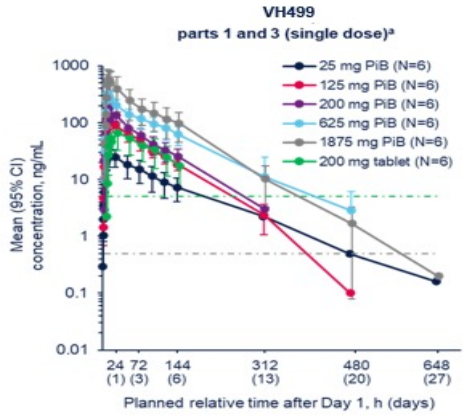


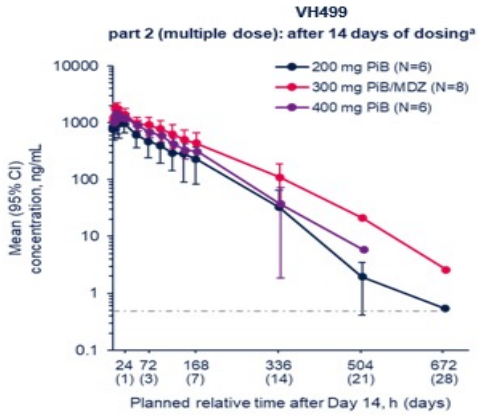
ViiV Pipeline
Core INSTIs and innovative ARV partners

CAB-ULA	VH-184	VH-310	VH-499	N6LS	VH 079

VH499 (capsid inhibitor) selected to progress to late-stage development

- Demonstrated exposures that exceeded anticipated therapeutic target
- Well tolerated after single and multiple oral doses
- Phase 2a study is investigating the antiviral effect, safety, tolerability, and PK in ART-naïve adults living with HIV-1
- Selected partner with INSTI for Q2M self-administered regimen





VH-499 selected to partner with an INSTI for a Q1-2M self-administered regimen[1–3]

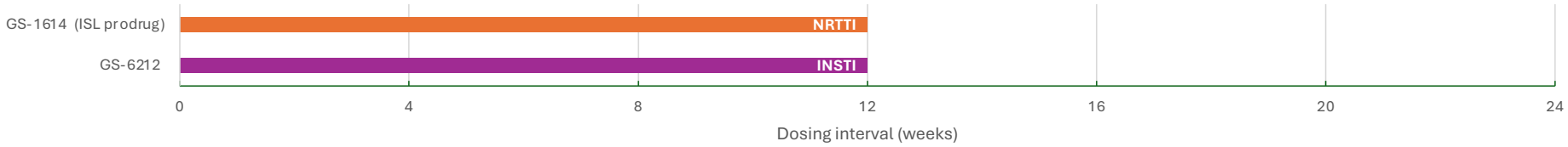
See notes for footnotes

ALT, alanine aminotransferase; **AST,** aspartate aminotransferase; **BMI,** body mass index; **CYP3A4**, cytochrome P450 3A; **FTiH,** first time in human **LDL-c,** low-density lipoprotein cholesterol; **MDZ, midazolam; PiB,** powder-in-bottle, **TC,** triglycerides; **ULN,** upper limit of normal

1. Wang C, et al. AIDS 2024 Poster WEPEA0272; **2.** Thakkar N, et al. AIDS 2024 Poster WEPEB105; **3.**Griesel R, et al. AIDS 2024 Poster THPEB093.

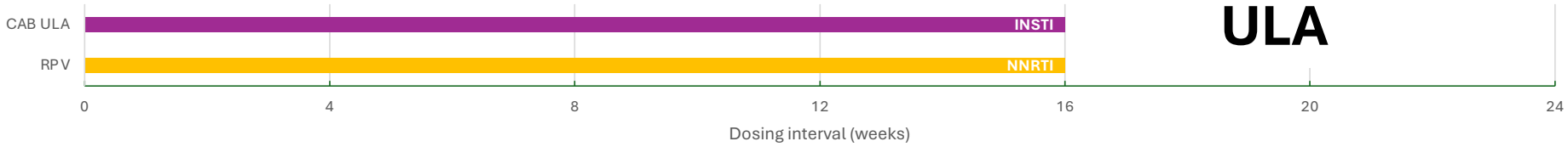
Q3M

Q3M


GS-1614 (ISL prodrug)
GS-6212
NRTTI
INSTI
0
4
8
12
16
20
24
Dosing interval (weeks)

Q4M

Q4M


CAB ULA
RPV
INSTI
NNRTI
ULA
0
4
8
12
16
20
24
Dosing interval (weeks)

ViiV Pipeline

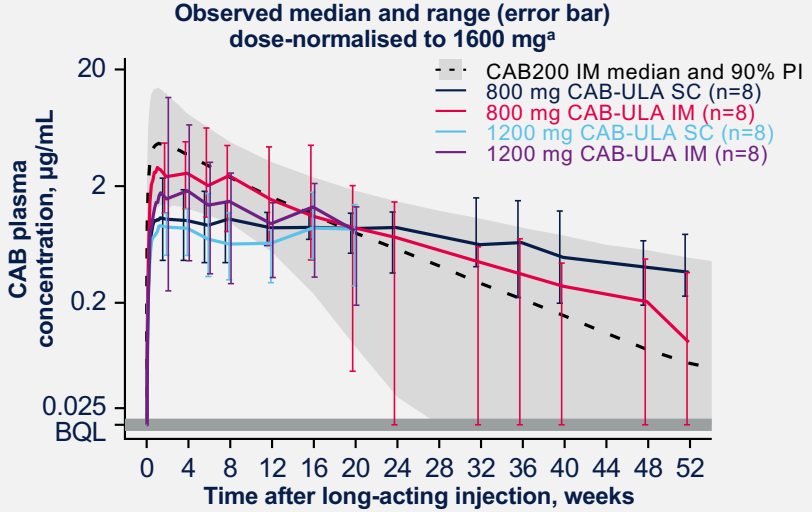
Core INSTIs and innovative ARV partners

CAB-ULA | VH-184 | VH-310 | VH-499 | N6LS | VH 079

Ultra long-acting CAB exhibits a PK profile that supports 3x/year dosing[1]

A new CAB-ULA formulation was administered SC or IM in an open-label, single-dose, dose-escalation Phase I study[1]

- CAB-ULA exhibited **slower absorption and longer $t_{1/2}$** than the CAB200 IM (currently approved CAB formulation[2]), with **flatter PK profiles[1]**
- **CAB-ULA $t_{1/2}$** for **SC** and **IM** was predicted to **be >6x and >2x the $t_{1/2}$ of CAB200 IM**, respectively[1,2,b]
- **CAB-ULA IM was better tolerated than SC** and was **comparable to the currently approved CAB200 IM ISR** profile[2], despite higher single doses of CAB-ULA[1]



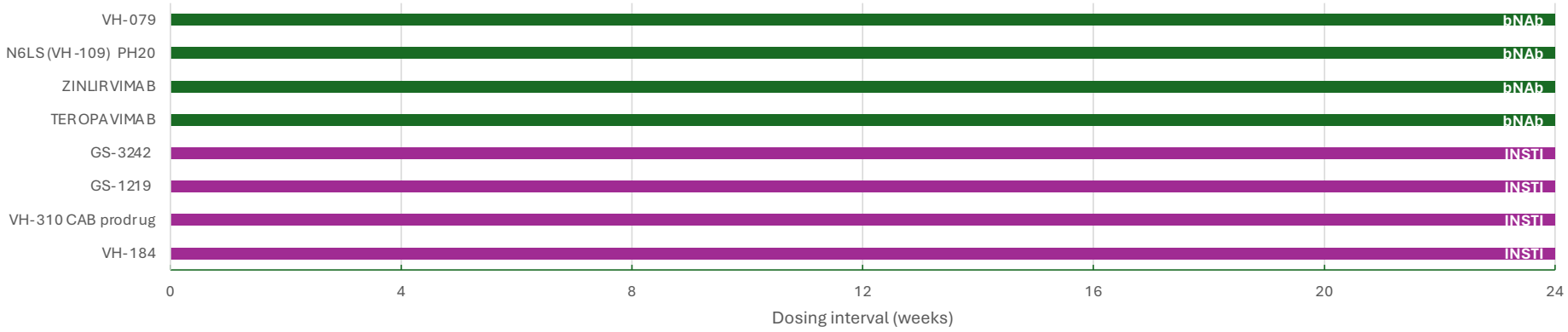
The new CAB-ULA formulation exhibited favourable tolerability and safety, with a PK profile that supports dose intervals of ≥4 months[1]

[a]Error bars before Week 2 are not displayed for visibility [b]Current follow-up time is insufficient to calculate final $t_{1/2}$ value for CAB-ULA
BQL, below quantification limit of 0.025 µg/mL; **ISR,** injection-site reaction; **n**, number of participants with valid PK parameters; **PI**, prediction interval
PK, pharmacokinetics; $t_{1/2}$, half-life

1. Han K et al. CROI 2024 Presentation 130
2. Vocabria EU SmPC. March 2024

Q6M

Q6M



O23: Efficacy and safety analysis of lenacapavir with broadly neutralising antibodies, teropavimab and zinlirvimab, in people with HIV-1 highly sensitive to one or both broadly neutralising antibodies

Paul P Cook, *Division of Infectious Diseases and Global Public Health, University of California, San Diego, CA, USA*

P037	**Correlation of baseline phenotypic sensitivity with virological response to VH3810109 (N6LS) in BANNER** *Margaret Gartland, Peter Leone, Judah Abberbock, Kathryn Brown, Paul Wannamaker, Rulan Griesel, Viviana Wilches, Jan Losos (Durham, NC, USA)*
P208	**VH3810109 (N6LS) administration dose-responsively enhances anti-HIV antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) activity in ex vivo models** *Michael Keegan, Margaret Gartland, Saikat Chakraborty, Judah Abberbock, Wilson Chen, Paul Wannamaker, Peter Leone, Jan Losos, Richard Dunham (London, UK)*

ViiV Pipeline
Core INSTIs and innovative ARV partners

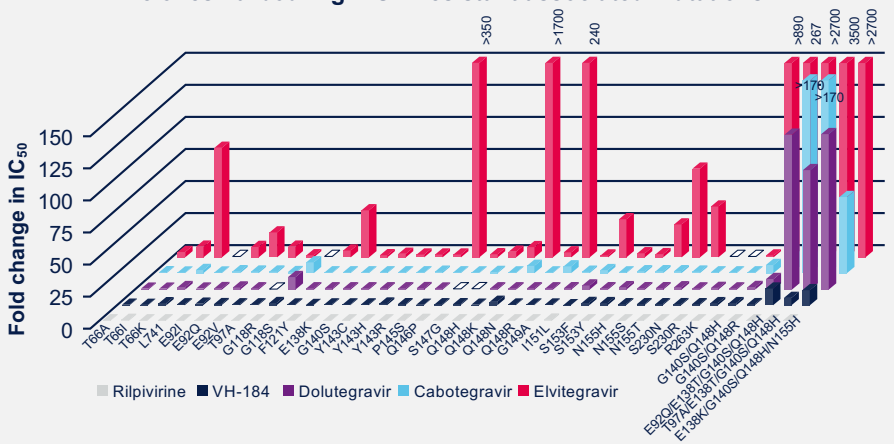
CAB-ULA | VH-184 | VH-310 | VH-499 | N6LS | VH 079

VH-184 is a potent third-generation INSTI with a resistance profile distinct from prior INSTIs

Phase I, first-time-in-human study and antiviral activity in vitro[1, 2]

- Early findings support the **safety of VH-184** with mild AEs[1]
- VH-184 demonstrated **potent *in vitro* antiviral activity** that was comparable to DTG and CAB and a resistance profile that **retained antiviral activity against second-generation INSTI-resistant isolates**[2]

Antiviral activity of VH-184 against a panel of HIV-1 molecular clones harbouring INSTI-resistant associated mutations[2*]



VH-184 is a third-generation INSTI with long-acting potential and a resistance profile distinct from second-generation INSTIs

*Clinical isolate populations and clonal variants originated from SAILING and DAWNING Phase III studies. Blank bars represent the variants which were not tested
AE, adverse event; **DTG,** dolutegravir; **IC50**, half-maximal inhibitory concentration

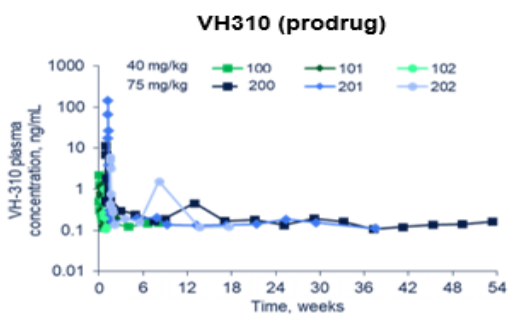
1. Rogg L, et al. AIDS 2024. Abstract XX
2. Seki T, et al. AIDS 2024. Abstract XX

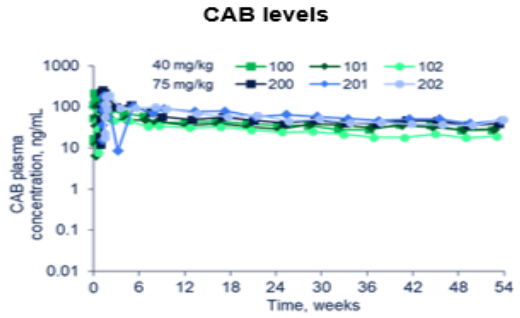
ViiV Pipeline

Core INSTIs and innovative ARV partners

CAB-ULA | VH-184 | **VH-310** | VH-499 | N6LS | VH 079

Following a single injection, VH310 (INSTI) delivers persistent CAB levels up to 1 year





- VH310 is a chemically modified version of cabotegravir that is less soluble, with a slower rate of dissolution. As a result it has a half life that substantially longer than cabotegravir.
- In vivo, VH310 is a rapidly converts to cabotegravir thus delivering therapeutic levels of cabotegravir with low levels of VH-310.
- First-time-in-human study to determine PK, safety, and dose will begin in early 2025
- These early data support development as a potential at least every-six-month antiretroviral agent for treatment and prevention

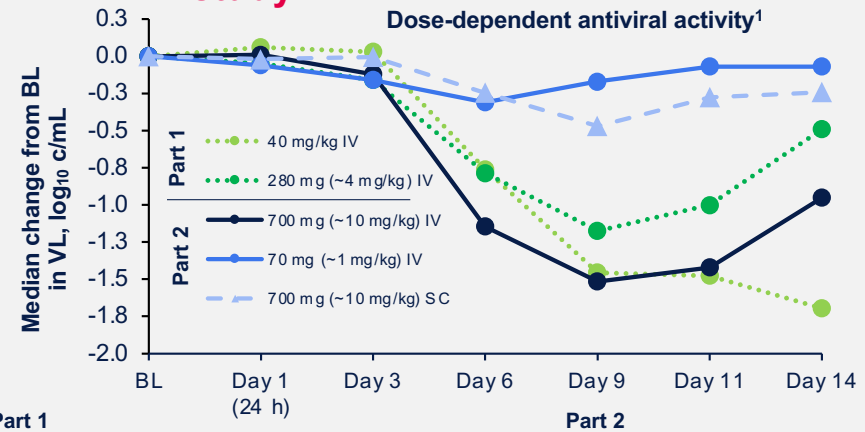
1. Baker M, et al. AIDS 2024 Poster WEPEA028; **2.** Invega Hafyera US Prescribing Information August 2021
3. Aristada US Prescribing Information February 2020

ViiV Pipeline
Core INSTIs and innovative ARV partners

CAB-ULA | VH-184 | VH-310 | VH-499 | **N6LS** | VH 079

N6LS (VH-109), a potent novel bNAb with ultra long-acting potential showed robust antiviral efficacy in the BANNER study[1]

- N6LS (VH-109) demonstrated **broad and potent neutralising activity** *in vitro*[2];
  - Neutralisation of up to 98% of viral strains*[2]

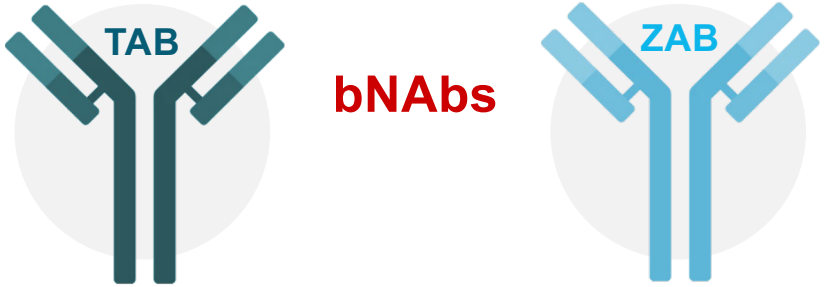


	Part 1		Part 2		
Viral dynamic measures, median (range)[1]	**N6LS 40 mg/kg IV (n=8)**	**N6LS 280 mg IV (~4 mg/kg*) (n=6)**	**N6LS 700 mg IV (~10 mg/kg*) (n=16)**	**N6LS 70 mg IV (~1 mg/kg*) (n=16)**	**N6LS 700 mg SC† (~10 mg/kg*) (n=16)**
Viral nadir from BL, log_{10} c/mL	−1.72 (−2.60, −0.60)	−1.18 (−2.18, −0.30)	−1.54 (−2.22, −0.41)	−0.43 (−1.29, −0.12)	−0.50 (−2.13, −0.09)
Time to viral nadir, days	16 (5–21)	9 (7–16)	9 (6–27)	7 (2–23)	9 (1–50)
Time to viral rebound among responders, days	35 (12–78) [n=8]	18 (14–29) [n=5]	22 (14–43) [n=14]	13 (10–22) [n=7]	17 (11–63) [n=8]

*For a 70 kg individual; †Lower exposures observed with SC vs IV administration were due to first-pass lymphatic **elimination**
BL, baseline; **IV,** intravenous; **VL,** viral load

1. Leone P, et al. CROI 2024. Oral 117

Teropavimab and Zinlirvimab

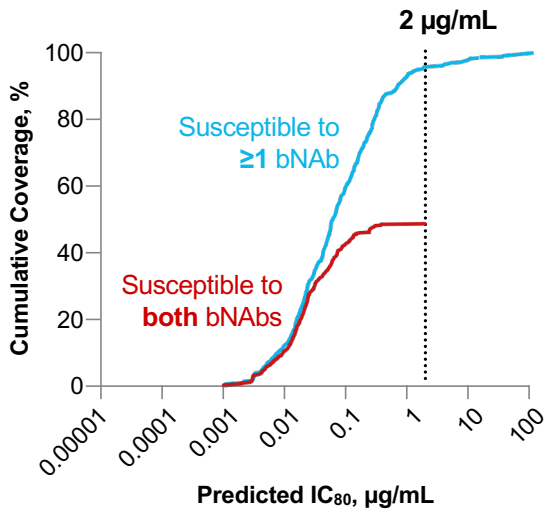


CD4-binding site of gp120[1,2]	Target	V3 glycan of HIV-1 Env[1,2]

Dosing

Extended half life of combination may allow for **6-monthly dosing**[1,2]

bNAb Susceptibility Breadth[2,a]



The efficacy and safety of TAB + ZAB + LEN have been evaluated in a **Phase 1b proof-of-concept study**[2]

Approximately **50%** of clade B viruses are highly susceptible to **both** TAB and ZAB, while **over 90%** are highly susceptible to **either** TAB or ZAB[3]

[a]Data from CATNAP CombiNAber

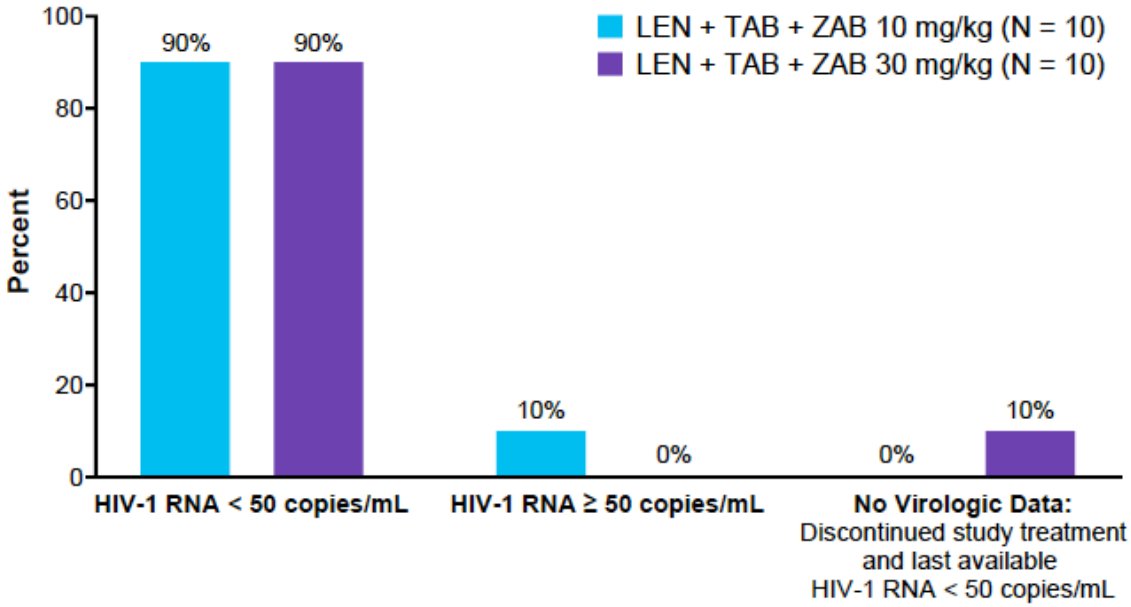
bNAb, broadly neutralizing antibody; IC, inhibitory concentration; TAB, teropavimab; ZAB, zinlirvimab

1. Gautam R, et al. *Nat Med* 2018; 24(5): 610-6; 2. Eron J, et al. CROI, 2024, Oral 120; 3. Selzer L, et al. CROI 2023. Poster 580

LENACAPAVIR. MAINTENANCE OF VIROLOGICAL SUPPRESSION SQ EVERY 6 MONTHS. Phase 1b

CROI 2023 Conference on Retroviruses and Opportunistic Infections
Seattle, US 19-22 February

Lenacapavir with bNAbs Teropavimab (GS-5423) and Zinlirvimab (GS-2872) Dosed Every 6 Months in People with HIV



- 18 out of 20 participants maintained viral suppression on study regimen through Week 26.
- One participant withdrew[1] at Week 12 with HIV-1 RNA < 50 copies/mL.
- One participant had a confirmed virologic rebound at Week 16 and was resuppressed on baseline oral ART.

Of 124 screened participants, 55 were sensitive to both bNAbs

Eron J et al. CROI 2023, Seattle. Abstract 193.

Phase 2: Investigational LEN + TAB + ZAB in VS PWH (GS-US-536-5939)[1]

‡

LEN with bNAbs, TAB and ZAB, Dosed Every 6 Months in PWH

N ≈ 83[1]

VS PWH aged 18–65 years[1]

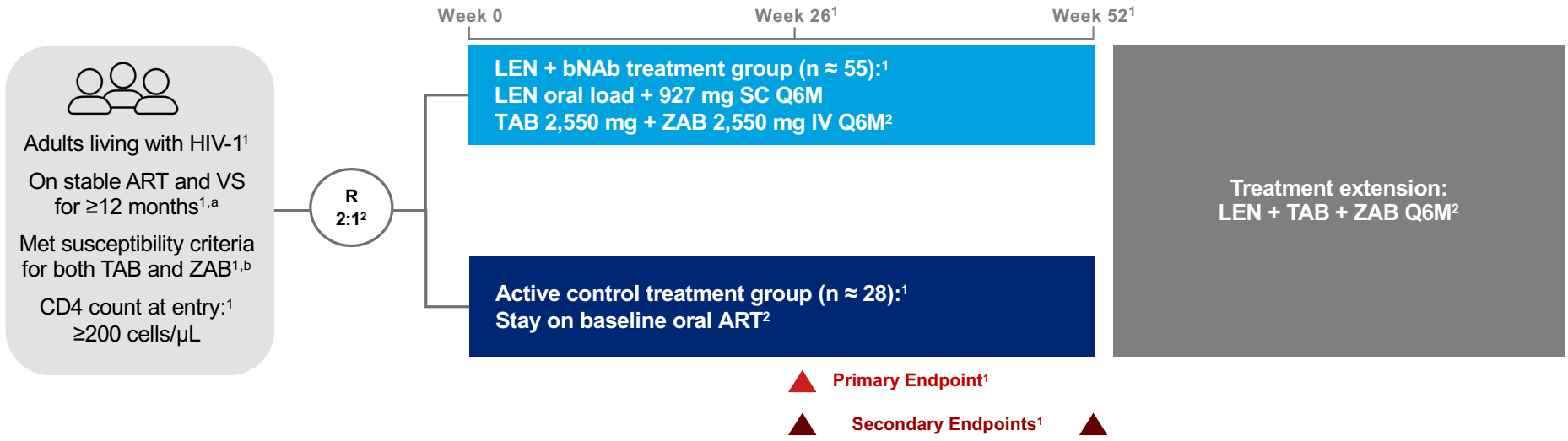
Outcomes[1]

Primary: HIV-1 RNA ≥50 c/mL at Week 26 (FDA snapshot)

Key secondary: Safety and tolerability, PK

2023–ongoing (fully enrolled)[1]

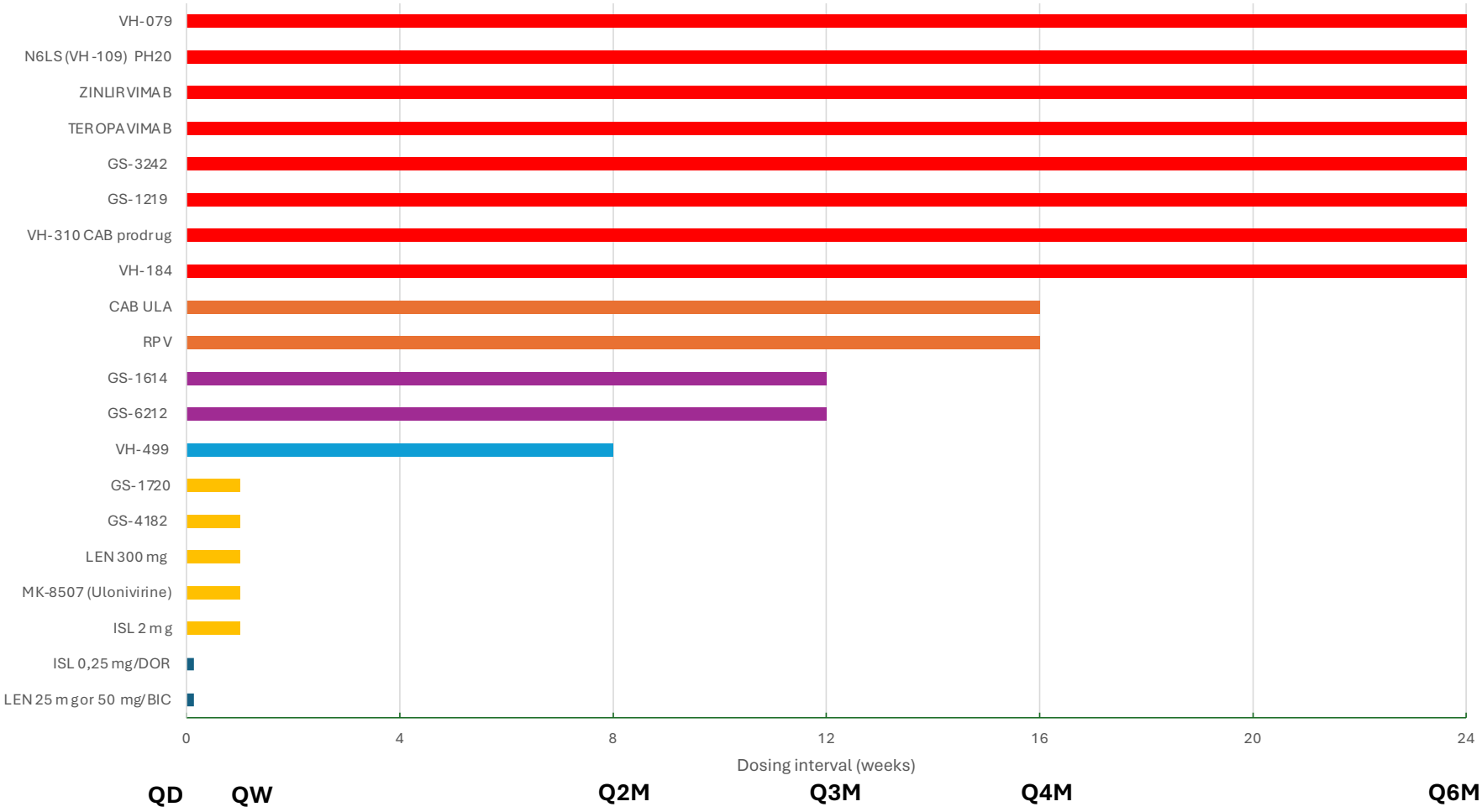
Study sites: United States, Australia, Canada and Puerto Rico[1]



[a]Virologic elevations of ≥50 c/mL (transient detectable viremia or "blips") prior to screening are acceptable;[1]
[b]Susceptibility defined as IC90 ≤2 µg/mL to each antibody by PhenoSense Monoclonal Antibody Assay (Monogram Biosciences)[2]
IC, inhibitory concentration; Q6M, every 6 months; TAB, teropavimab; VF, virologic failure; VS, virologically suppressed; ZAB, zinlirvimab

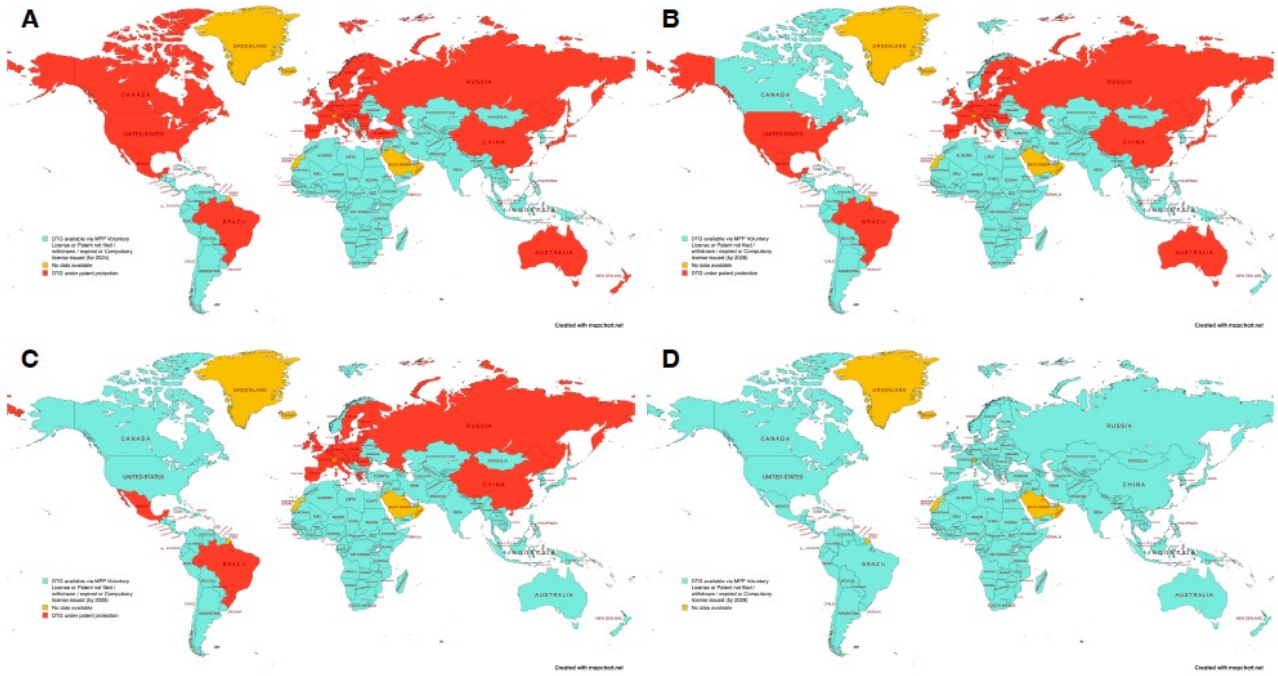
1. NCT05729568. https://clinicaltrials.gov/ct2/show/NCT05729568 (accessed July 14, 2023); 2. Data on file. Gilead Sciences, Inc.

INTERVAL*



*For a number of drugs the interval is aspirational, still under investigation

Challenges for Novel Antiretroviral Development in an Era of Widespread TLD Availability



2029

Figure 1. World map of dolutegravir (DTG) patent expiry. *A*, DTG access map for 2024. *B*, DTG access map for 2026. *C*, DTG access map for 2028. *D*, DTG access map for 2029. (Maps made using https://www.mapchart.net/.)

CID 2024

Table 1. Summary of Key Requirements for Widespread Use of Antiretroviral Therapy

	Benchmark	TDF/3TC/DTG	DOR/ISL	CAB/RPV
1	Efficacy in treatment-naive individuals	Unsurpassed	Likely noninferior to DTG + 2NRTI	Noninferior to DTG + 2NRTI
2	High genetic barrier to resistance	Yes	No	No
3	Safe in hepatitis B coinfection (hepatitis B surface antigen or hepatitis B virus DNA positive)	Yes	No	No
4	Effective against human immunodeficiency virus type 2	Yes	No	No
5	Safely coadministered with anti-tuberculosis medication	Yes	No	No
6	Acceptable safety in pregnancy	Yes	Insufficient data	Insufficient data
7	Course price per person per year	<45 (generic)	DOR $22 673–$5966 (no data for ISL)	$20 643–$11 771
8	Availability in long-acting formulations	Under investigation	Studies held: ISL with lenacapavir under investigation	Available in injectable monthly or 2-monthly formulation

Abbreviations: 3TC, lamivudine; CAB, cabotegravir; DOR, doravirine; DTG, dolutegravir; ISL, islatravir; NRTI, nucleoside reverse-transcriptase inhibitor; RPV, rilpivirine; TDF, tenofovir-disoproxil.

CID 2024

Why Invest in New Antiretrovirals Beyond Generic TLD?

- **Clinical Superiority**
  - Higher barrier to resistance and superior efficacy in hard-to-treat populations.
  - Safer profiles in special populations (pregnancy, elderly, renal/hepatic impairment).
- **Patient-Centric Innovations**
  - Ultra-long dosing intervals (up to 6–12 months) for enhanced convenience.
  - Discreet delivery options (implants, patches, self-administered injectables).
- **Public Health Benefits**
  - Improved adherence and viral suppression in vulnerable populations.
- **Healthcare System Impact**
  - Fewer clinic visits and simplified logistics for low-resource settings.

New Treatments and Future Combinations

- **Expansion of long-acting therapies reducing the frequency of administration and improving convenience**
- **ORAL QW**
- **Emergence of dual therapy regimens that minimize drug exposure while maintaining effectiveness**
- **Uncharted territory. New combinations INSTI-free, NRTI free. Benefits?**

Aknowledgements

- Susan Chuck
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- Andrew Hill