WEPEB106

Phase 1, open-label study to evaluate the drug interaction between MK-8527, an HIV-1 nucleoside reverse transcriptase translocation inhibitor, and the oral contraceptive levonorgestrel/ethinyl estradiol in healthy adult female participants

Russ P. Carstens[1]; Yash Kapoor[1]; Graigory C. Garrett[1]; Arinjita Bhattacharyya[1]; Sandra Pagnussat[2]; Ryan Vargo[1]; S. Aubrey Stoch[1]; Gillian Gillespie[1*]

[1]Merck & Co., Inc., Rahway, NJ, USA; [2]QPS-Miami Research Associate, Miami, FL, USA.

*Presenting author

Background

- HIV remains a worldwide public health issue: globally, ~39 million individuals (53% of whom are females) are infected; ~1.3 million new infections (46% in females) occurred in 2022[1]
- MK-8527 is a novel nucleoside reverse transcriptase translocation inhibitor (NRTTI) that is phosphorylated intracellularly to its active triphosphate form, functions as a potent and specific inhibitor of HIV-1 reverse transcriptase,[2-4] and is currently in phase 2 clinical development for once monthly (QM) dosing as pre-exposure prophylaxis[5]
  - Preclinical and clinical pharmacokinetic (PK) properties of MK-8527 support extended duration dosing of once weekly (QW) and QM[2,3]
  - In adults without HIV, single (0.5-200 mg) and multiple (QW for 3 weeks; 5-40 mg) doses of MK-8527 were generally well tolerated[3]
  - In people with HIV-1 who were naive to treatment, single doses of MK-8527 as low as 0.5 mg achieved ≥1.0 log_{10} copies/mL decreases in HIV-1 RNA 7 days after administration[4]
- Hormonal contraceptives are commonly used in many countries[6]; however, significant drug-drug interactions (DDIs) can occur when used concurrently with some medications, including certain HIV antiretrovirals[7,8]

Objective

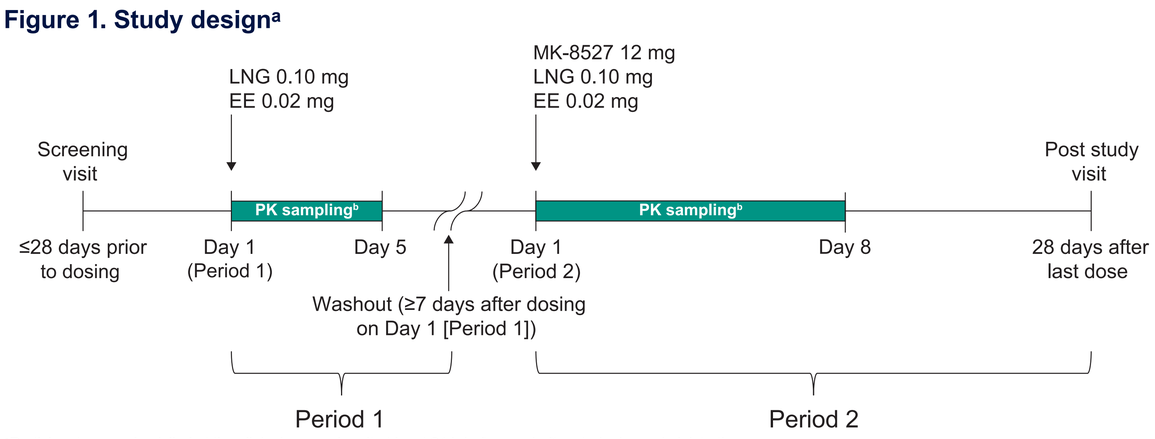
- This phase 1 clinical trial was conducted in adult female participants without HIV to evaluate any potential effects of MK-8527 on the PK of the oral combination hormonal contraceptive levonorgestrel (LNG)/ethinyl estradiol (EE)

Methods

Study design

- Open-label, 2-period, fixed-sequence DDI trial (MK-8527-006) to assess the effects of a single oral dose of MK-8527 on the PK of a single dose of LNG and EE (**Figure 1**)
  - Eligible participants:
    - Healthy adults (18 to 70 years of age, inclusive) assigned female sex at birth
    - Postmenopausal or at least 6 weeks postsurgical bilateral oophorectomy
    - Body mass index of 18.5-32 kg/m^2
  - Key exclusion criteria:
    - Pre-existing health conditions deemed clinically significant by the investigator to advise against participation in the study, including contraindications to the use of oral hormonal contraceptives
    - Estimated glomerular filtration rate ≤80 mL/min (Chronic Kidney Disease Epidemiology Collaboration equation) at the screening visit
    - Positive test result for hepatitis B virus surface antigen, hepatitis C virus antibodies, or HIV
- In each period, participants fasted from all food and drink, except water, for ≥8 h before and ≥4 h after study drug administration

Figure 1. Study design[a]



[a]Participants were domiciled at the clinical research unit at least 24 h before and after study drug administration.

[b]Plasma for measurement of LNG, EE, and MK-8527 concentration was collected pre dose and at 0.5, 1, 1.5, 2, 4, 6, 8, 24, 48, and 72 h post dose (LNG and EE in Period 1; LNG, EE, and MK-8527 in Period 2). Additional samples were collected at 96 h (LNG and MK-8527 only) and 168 h (MK-8527 only) post dose.

Assessments and analysis

- PK parameters assessed were area under the concentration-time curve from 0 h to infinity ($AUC_{0-\infty}$), maximum concentration (C_{max}), time to maximum plasma concentration (T_{max}), and terminal half-life ($t_{1/2}$)
- Safety and tolerability were assessed by standard clinical evaluations, including adverse event (AE) reporting, vital sign monitoring, laboratory values (including hematological parameters), and electrocardiograms
- Individual $AUC_{0-\infty}$ and C_{max} of LNG and EE values were natural log transformed prior to analysis and evaluated separately using a linear mixed effects model, with fixed effects term for treatment
  - The criteria for PK similarity were the true geometric mean ratio (GMR) for $AUC_{0-\infty}$ of LNG and EE contained between 0.8 and 1.50

Results

Participants

- 14 participants were enrolled (**Table 1**), and all (100%) completed the study

Table 1. Participant demographics and baseline characteristics

Parameter	N = 14
Female, n (%)	14 (100)
Age, median (range), years	61 (51-65)
Body mass index, median (range), kg/m^2	25.8 (22.5-31.7)
Race, n (%)	
White	14 (100)
Ethnicity, n (%)	
Hispanic or Latino	14 (100)

PK analysis of LNG

- The 90% CI for the true GMR of $AUC_{0-\infty}$ of LNG was contained within the protocol-specified bounds for similarity (0.80, 1.50) and there was no clinically meaningful change in T_{max} or $t_{1/2}$ with or without MK-8527 (**Figure 2**, **Table 2**)

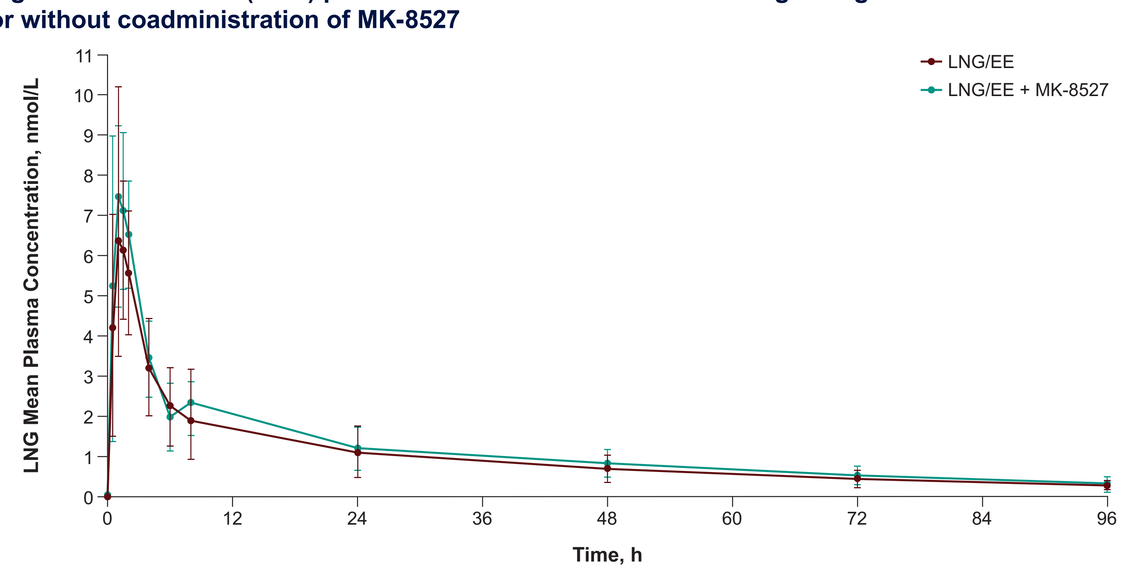
Table 2. Summary of plasma PK of LNG following a single dose of LNG/EE with or without coadministration of MK-8527

Parameter	LNG/EE N = 14	MK-8527 + LNG/EE N = 14	(MK-8527 + LNG/EE)/(LNG/EE)	
	LNG GM (95% CI)	LNG GM (95% CI)	GMR (90% CI)	%CV[a]
$AUC_{0-\infty}$, nmol/L·h	101 (78.8-131)	124 (101-151)	1.22 (1.13-1.32)	11.5
C_{max}, nmol/L	6.54 (5.28-8.10)	7.84 (6.46-9.53)	1.20 (1.09-1.32)	13.8
T_{max}, h (median [range])	1.25 (1.00-2.00)	1.00 (0.50-2.00)	NA	NA
$t_{1/2}$, h (GM [%GCV])	37.4 (27.6)	38.4 (24.8)	NA	NA

CV, coefficient of variation; GCV, geometric coefficient of variation; GM, geometric mean; NA, not applicable.

[a]Within-participant CV (%) was estimated based on the elements of the variance-covariance matrix: $\%CV = 100*\sqrt{([\sigma^2_A + \sigma^2_B - 2*\sigma_{AB}]/2)}$.

Figure 2. Mean linear (± SD) plasma concentration of LNG following a single dose of LNG/EE with or without coadministration of MK-8527



PK analysis of EE

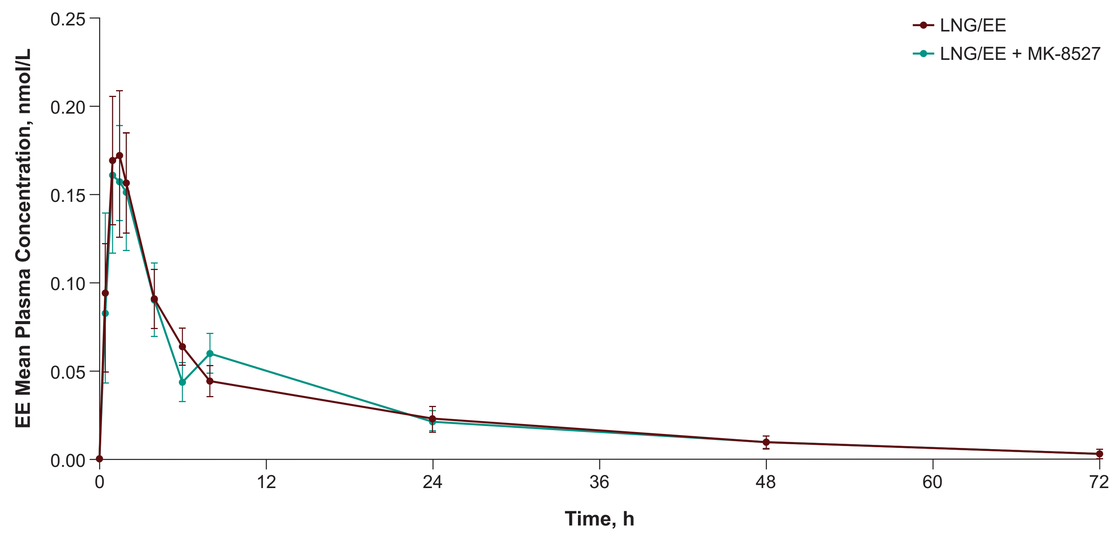
- The 90% CI for the true GMR of $AUC_{0-\infty}$ of EE was contained within the protocol-specified bounds for similarity (0.80, 1.50) and the T_{max} and $t_{1/2}$ were similar with or without MK-8527 (**Figure 3, Table 3**)

Table 3. Summary of plasma PK of EE following a single dose of LNG/EE with or without coadministration of MK-8527

Parameter	LNG/EE N = 14	MK-8527 + LNG/EE N = 14	(MK-8527 + LNG/EE)/(LNG/EE)	
	EE GM (95% CI)	EE GM (95% CI)	GMR (90% CI)	%CV[a]
$AUC_{0-\infty}$, nmol/L·h	1.83 (1.60-2.10)	1.83 (1.60-2.09)	1.00 (0.95-1.05)	7.8
C_{max}, nmol/L	0.177 (0.158-0.198)	0.166 (0.145-0.191)	0.94 (0.87-1.02)	11.7
T_{max}, h (median [range])	1.25 (0.50-2.00)	1.25 (1.00-2.00)	NA	NA
$t_{1/2}$, h (GM [%GCV])	17.7 (20.5)	16.6 (30.8)	NA	NA

[a]Within-participant CV (%) was estimated based on the elements of the variance-covariance matrix: $\%CV = 100*\sqrt{([\sigma2A + \sigma2B - 2*\sigma AB]/2)}$.

Figure 3. Mean linear (± SD) plasma concentration of EE following a single dose of LNG/EE with or without coadministration of MK-8527



Safety

- No participants reported serious AEs or discontinued study treatment due to an AE
- Five participants (36%) reported AEs, all mild in severity
  - Four AEs (headache [n = 1], leukopenia [n = 2], dizziness [n = 1]) were considered treatment-related by the investigator
    - Both cases of leukopenia were mild and transient, and the total lymphocyte, neutrophil, and monocyte counts remained within the respective normal ranges in both cases (**Table 4**)
    - One report of leukopenia was in a participant with a prior medical history of this condition, who showed a decline in leukocyte counts from screening to pre-dose in Period 2 (case 2, **Table 4**)
  - One AE (gingival pain) was considered not related to study treatment
- No additional clinically meaningful changes in electrocardiograms, vital signs, or safety laboratory values were noted

Table 4. Hematology summary of 2 cases of leukopenia

Case	Cell type (normal range)[a]	Screening	Period 1, pre-dose	Period 2, pre-dose	Period 2, 7 days post-dose	Follow-up
1	Neutrophils (1.5-7.8)	2.3	2.5	2.5	2.1	2.3
	Lymphocytes (0.8-4.1)	1.5	1.7	1.5	1.2	1.4
	Monocytes (0.2-1.1)	0.4	0.4	0.5	0.3	0.3
	Leukocytes (3.8-10.8)	4.4	4.7	4.6	**3.7 (3.6)**	4.1
2	Neutrophils (1.5-7.8)	2.6	1.8	2.0	1.7	1.9
	Lymphocytes (0.8-4.1)	1.8	1.6	1.3	1.0	1.6
	Monocytes (0.2-1.1)	0.2	0.3	0.2	0.2	0.2
	Leukocytes (3.8-10.8)	4.6	**3.7**	**3.5**	**2.9 (3.6)**	**3.7**

Red font indicates values outside the normal range.

[a]Values are 10^9 cells/L.

Conclusions

- The plasma PK of LNG and EE with or without administration of MK-8527 were similar
- Coadministration of MK-8527 and LNG/EE was generally well tolerated
- These results suggest that MK-8527 would be acceptable for coadministration with hormonal contraceptives containing LNG and/or EE

References

1. UNAIDS. 2023 fact sheet - global HIV statistics. Accessed May 1, 2024. https://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf
2. Raheem I et al. Discovery of MK-8527, a long-acting HIV nucleoside reverse transcriptase translocation inhibitor. Presented at: Conference on Retroviruses and Opportunistic Infections; March 3-6, 2024; Denver, CO.
3. Gillespie G et al. Safety and pharmacokinetics of MK-8527, a novel NRTTI, in adults without HIV. Presented at: Conference on Retroviruses and Opportunistic Infections; March 3-6, 2024; Denver, CO.
4. Carstens R et al. Single dose administration of MK-8527, a novel NRTTI, in adults with HIV-1. Presented at: Conference on Retroviruses and Opportunistic Infections; March 3-6, 2024; Denver, CO.
5. ClinicalTrials.gov. NCT06045507: Safety and Pharmacokinetic Study of Oral MK-8527 QM in Participants at Low-Risk for HIV-1 Infection (MK-8527-007). Accessed Apr 30, 2024. https://clinicaltrials.gov/ct2/show/NCT06045507
6. United Nations Department of Economic and Social Affairs. Contraceptive use by method 2019. Accessed Apr 30, 2024. https://www.un.org/development/desa/pd/sites/www.un.org.development.desa.pd/files/files/documents/2020/Jan/un_2019_contraceptiveusebymethod_databooklet.pdf
7. Landolt NK et al. Significant decrease of ethinylestradiol with nevirapine, and of etonogestrel with efavirenz in HIV-positive women. *J Acquir Immune Defic Syndr.* 2014;66(2):e50-2.
8. Sevinsky H et al. The effect of efavirenz on the pharmacokinetics of an oral contraceptive containing ethinyl estradiol and norgestimate in healthy HIV-negative women. *Antivir Ther.* 2011;16(2):149-56.

Acknowledgments

The authors thank all those who participated in this study. The contributions of the investigators and their staff are also gratefully recognized. Medical writing and/or editorial assistance was provided by Jared Cochran, PhD, of ApotheCom (Yardley, PA, USA). This assistance was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Funding for this research was provided by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Presented at the 25th International AIDS Conference (AIDS); July 22-26, 2024; Munich, Germany, and virtually