

Levonorgestrel-Containing Contraceptives: Comparison of Daily Doses and Exposure for Various Routes of Administration by an Integrated Population Pharmacokinetic Analysis



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Introduction

Women can choose among a number of contraceptives and administration routes containing the progestin levonorgestrel (LNG). This hormone is used as a component in contraceptives because of its influence on at least 2 mechanisms in preventing pregnancy: ovulation inhibition and thickening of the cervical mucus.

A direct comparison of LNG daily doses and exposure of these different products has not been made until recently [1]. LNG-containing contraceptives administered orally or as an implant act mainly via their systemic LNG exposure, whereas LNG administered via an intrauterine system (IUS) is released directly into the uterine cavity, resulting in lower systemic LNG concentrations.

All LNG-containing contraceptives included in this analysis are known to be safe and highly effective, despite the fact that they differ in administration route, daily LNG dose and systemic exposure. However, a comparison of daily dose and exposure would support decision making between products by health care providers and by the women themselves.

Results

An overview of the results is presented in Table 1. The highest daily (bioavailable) dose is provided by using the combined oral contraceptive, followed, in decreasing order, by the progestin-only pill and the implant (both similar daily bioavailable doses), and the IUSs LNG-IUS 20, LNG-IUS 12, and LNG-IUS 8. See Graph 1 for comparison of simulated *in vivo* release rates for the IUSs and the implant. This is in line with the comparison of the estimated LNG exposure (see Graph 2 for comparison of simulated LNG exposure).

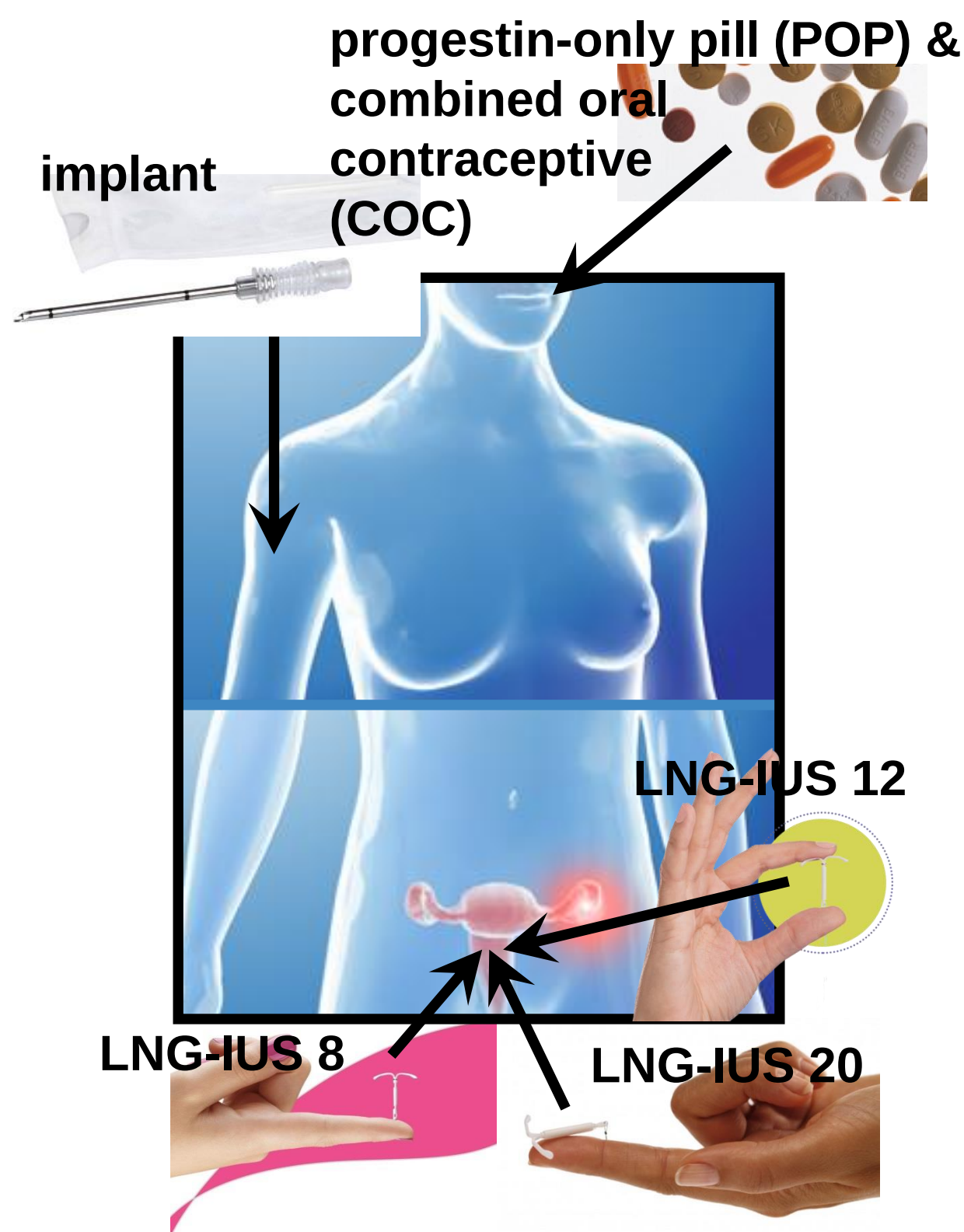
Objectives

- Compare typical LNG exposure for 3 IUSs, 2 oral contraceptives, and an implant, by simulating the exposure for the same treatment duration based on an integrated population PK (popPK) model.
- Compare absolute bioavailability and daily LNG doses by calculating *in vivo* release rates for the IUSs and implant based on the integrated popPK model.

Methods

For this analysis, data from 10 clinical pharmacology studies in healthy premenopausal women (n=3424) with 6 LNG-containing contraceptives, including intravenous (iv) data, were integrated: 3 intrauterine systems (IUSs; LNG-IUS 20 [Mirena®], LNG-IUS 12 [Kyleena®], and LNG-IUS 8 [Jaydess®/Skyla®]); 2 oral contraceptives (the progestin-only pill [Microlut®/Norgeston®] and the combined oral contraceptive [Miranova®]); and a subdermal implant (Jadelle®).

The integrated popPK analysis was performed by means of a nonlinear mixed-effects approach using NONMEM® software (Version 7.2.0). Simulations were performed using R software (version 3.2.0 or higher).

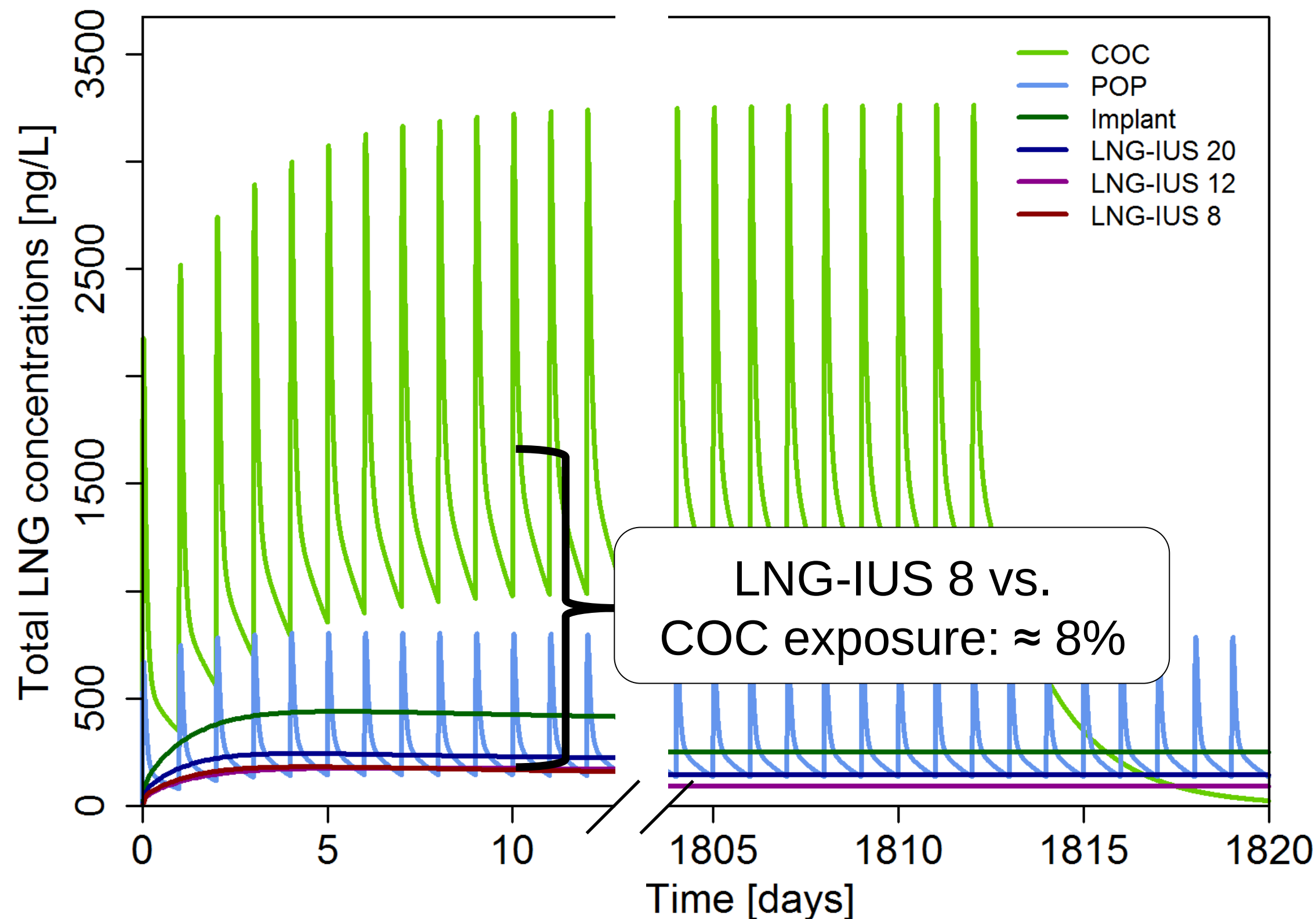
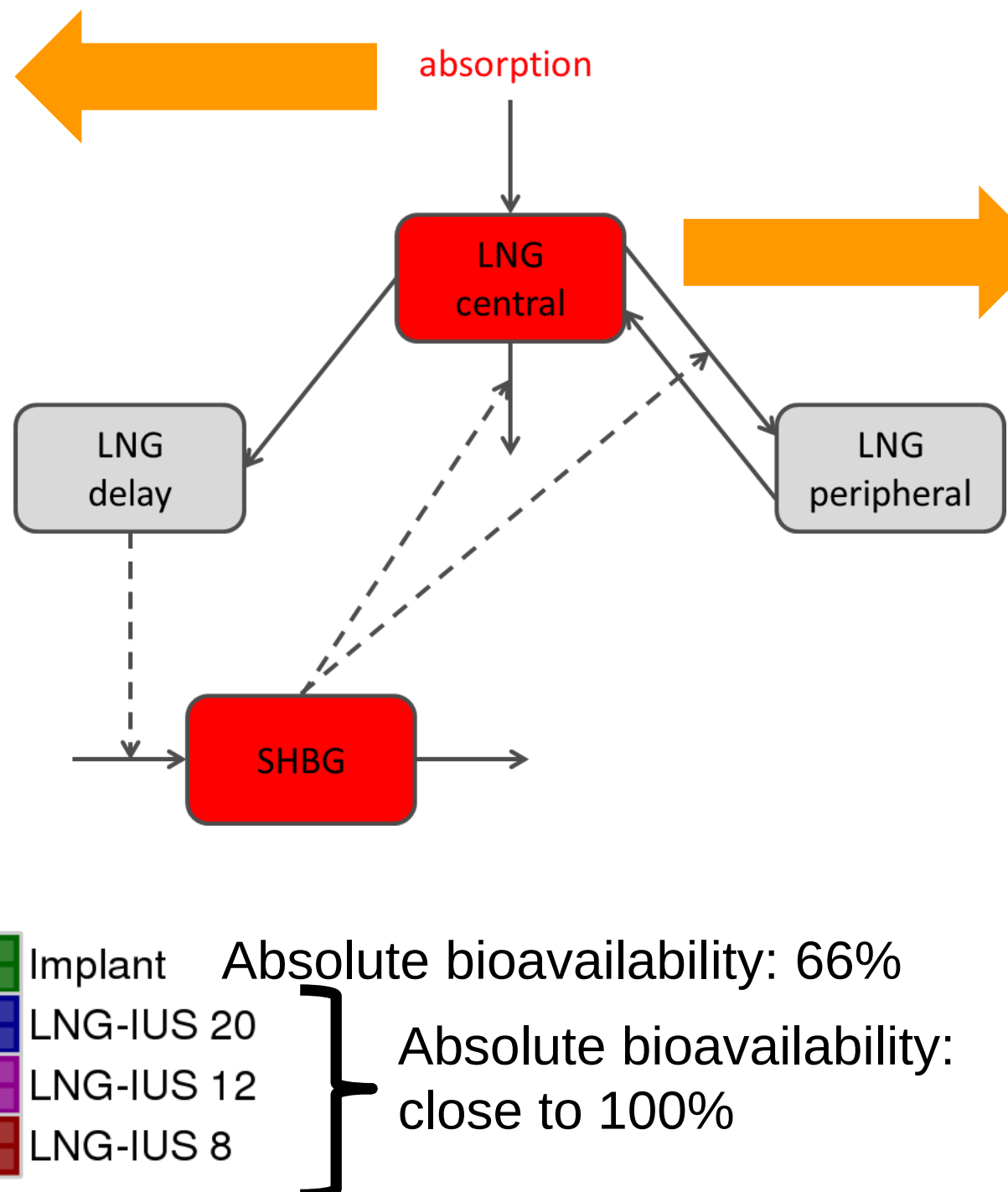
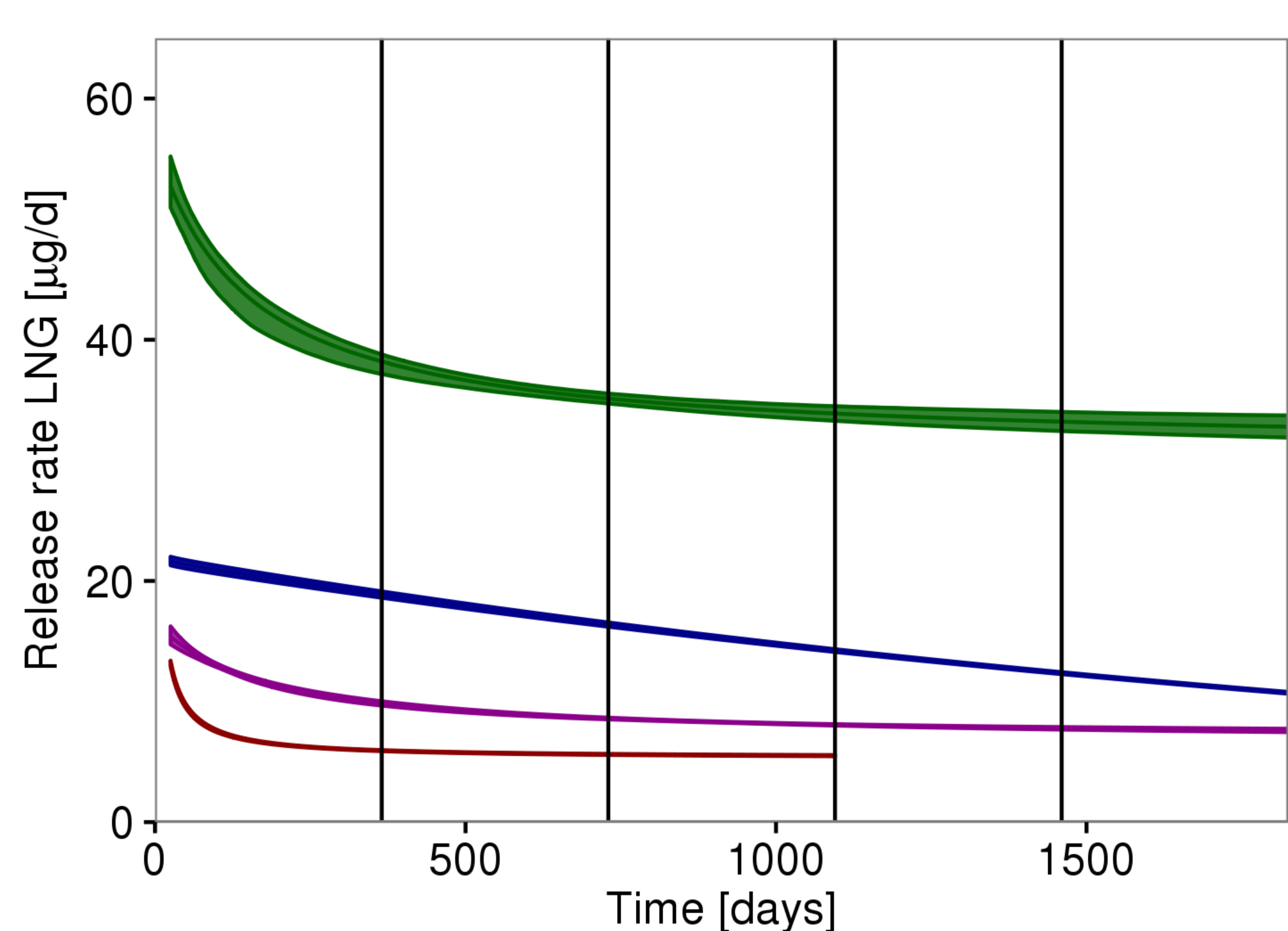


Product	Absolute bioavailability	Dose [µg]	Daily bioavailable dose [µg]	Exposure at steady-state [ng/L]
Combined oral contraceptive (COC)*	≈ 80%	100	≈ 80	1676 (1370-2050)
Progestin-only pill (POP)	≈ 80%	30	≈ 24	327 (281-380)

Table 1: Comparison of daily (bioavailable) doses and exposure of LNG.
In vivo release rates: typical (95% confidence interval (CI)). Exposure: geometric mean (95% CI). Initial: after 24 days. At the end (of period-of-use): 3 years (LNG-IUS 8), 5 years (implant, LNG-IUS 20, LNG-IUS 12). *combined with 20 µg ethinylestradiol.

Product	Absolute bioavailability	Initial <i>in vivo</i> release rate [µg/d]	Initial daily bioavailable dose [µg]	Initial exposure [ng/L]	At-the-end <i>in vivo</i> release rate [µg/d]	At-the-end daily bioavailable dose [µg]	At-the-end exposure [ng/L]
Implant	≈ 66%	53.0 (51.3-54.9)	≈ 35	413 (395-432)	32.8 (32.0-33.6)	≈ 22	259 (247-271)
LNG-IUS 20	Close to 100%	21.7 (21.4-21.9)	≈ 21	196 (189-203)	10.7 (10.7-10.8)	≈ 13	133 (127-139)
LNG-IUS 12	Close to 100%	15.4 (14.8-16.1)	≈ 15	152 (149-156)	7.59 (7.48-7.71)	≈ 7.5	84.8 (80.7-89.1)
LNG-IUS 8	Close to 100%	13.4 (13.2-13.6)	≈ 13	127 (124-130)	5.51 (5.47-5.55)	≈ 5.4	58.1 (55.4-60.8)

The LNG concentration of the LNG-IUS 8, the IUS with the lowest daily dose, decreased from approximately 8 % after 24 days to 3 % after 3 years, compared to exposure at steady-state for the COC.



Graph 1: Comparison of simulated *in vivo* release rates over 3 to 5 years of treatment.
Solid line: predicted release rate. Limits of shaded area: 5th and 95th percentile of simulations. Vertical lines: 1, 2, 3, and 4 years. Simulations are shown for time ≥24 days (only very few data in the initial phase).

Graph 2: Comparison of simulated typical LNG concentrations (initial phase and close to 5 years).
Assuming body weight = 65 kg and sex-hormone binding globulin baseline (SHBG) concentration = 60 nmol/L.

Conclusions

The integrated popPK analysis allowed a valid comparison of daily (bioavailable) LNG doses and systemic exposure for 6 LNG-containing contraceptives which may support decision making between products by health care providers and by the women themselves. The analysis revealed that the combined oral contraceptive provided the highest daily LNG dose and led to the highest systemic LNG exposure, whereas the IUSs, in particular LNG-IUS 8, provided the lowest daily LNG dose and led to the lowest systemic LNG exposure.

References

[1] Reinecke I, Hofmann B, Mesic E, Drenth HJ, Garmann D. An Integrated Population Pharmacokinetic Analysis to Characterize Levonorgestrel Pharmacokinetics After Different Administration Routes. The Journal of Clinical Pharmacology (2018), 58:12, 1639-1654