IN SILICO DESIGN OF A MICROARRAY PATCH AS A MULTIPURPOSE PREVENTION TECHNOLOGY

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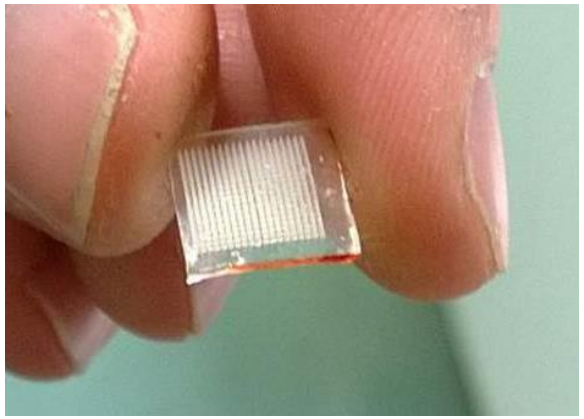
Long-Acting/Extended Release Antiretroviral Resource Program

Conflicts of interest

- No conflicts to declare

Background

- Co-administration of antiretrovirals (ARVs) and contraceptives as a multipurpose prevention strategy can potentially simplify dosing
- Long-acting (LA) strategies could help reduce the problems associated with pill fatigue and sub-optimal adherence
- ARVs are currently being developed as intramuscular LA formulations
- Intradermal delivery through microneedle array patches represents an alternative strategy for LA administration



Microneedle array patches (MAPs)

- Consist of micron-sized needle arrays of varying sizes capable of disrupting stratum corneum
- Capable of local and systemic delivery, blood-free with painless application
- Provide patient friendly, low cost and minimally invasive route for drug delivery
- Deliver intact nanoformulations that form a depot in the upper skin layers

Hydrogel MAPs

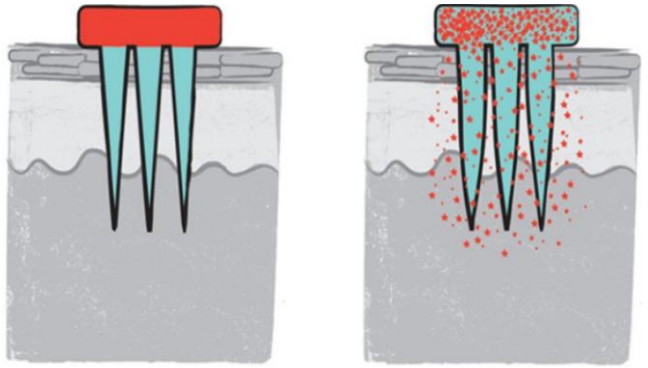


Fig. 1 *Fig. 2*

Dissolving MAPs

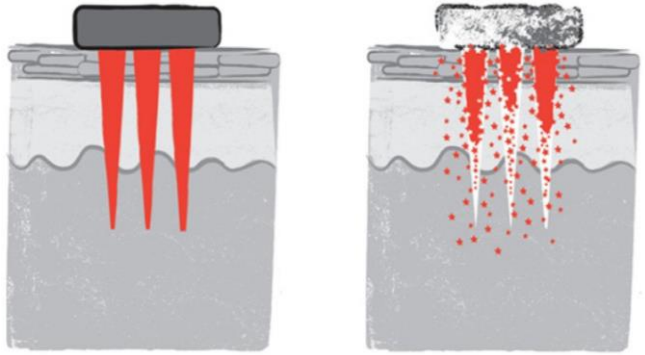


Fig. 1 *Fig. 2*

Image: PATH

PATH - http://www.path.org/publications/files/VAC_hiv_prep_poster.pdf

Aims

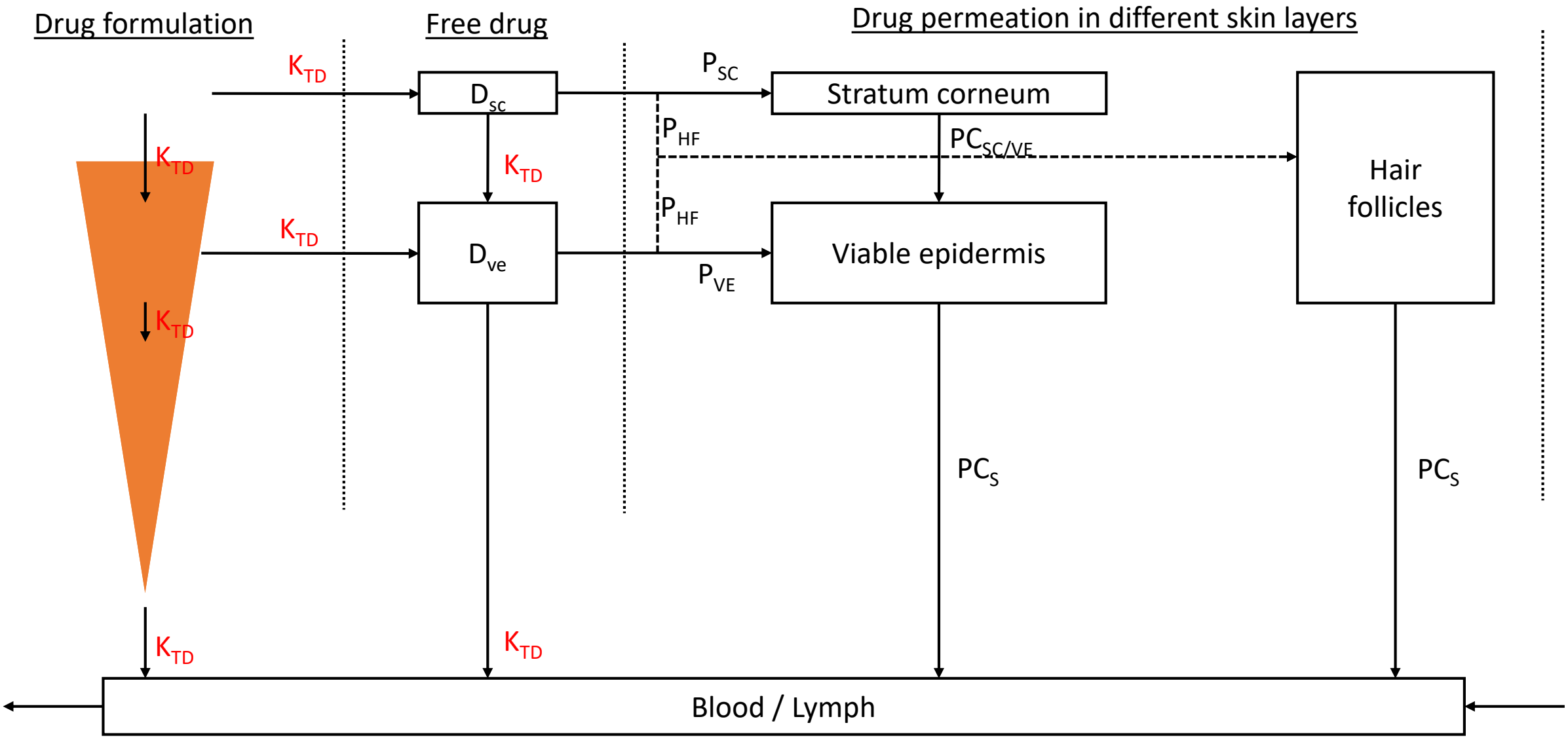
- Design an intradermal physiologically-based pharmacokinetic (PBPK) model to simulate pharmacokinetics of cabotegravir (CAB) and norelgestromin (NGMN) resulting from administration through MAPs
- Predict pharmacokinetics of CAB and NGMN weekly and monthly MAPs to identify minimum dose and release rates in humans with C_{trough} over target concentrations:
  - 10 mg PO C_{trough} for cabotegravir
  - Target range of 0.6 to 1.2 ng/ml[1] for NGMN

[1] Larry S. Abrams et al. Fertility and Sterility. 2002;77(2), Suppl 2:S3-S12

Methods

- A whole-body compartmental PBPK model (Simbiology, MATLAB 2018a) representing various organs and tissues was used in this study
- One hundred virtual healthy adult women were considered as the study population (74 kg (SE 0.42), 1.62 m (SE 0.21), 29.2 kg/m^2 (SE 0.17))
- PBPK model was qualified for existing cabotegravir(CAB) oral and intramuscular (IM) LA formulations and norelgestromin (NGMN) transdermal patch
- Intradermal model was qualified against available data of rilpivirine MAPs in rats
- MAPs were conical in shape with a dimension of 600 µm in depth, 300 µm base diameter and a dose loading of 32.7 mg of formulation per 8 cm^2

Intradermal model



P – permeability , PC – partition coefficient K_{TD} – release rate from the formulation

Cabotegravir PBPK qualification

Table PBPK qualification of intramuscular cabotegravir in healthy adults

	Clinical			Simulated			% difference simulated vs. clinical		
Drug	**C_{max}**	**AUC**	**C_{trough}**	**C_{max}**	**AUC**	**C_{trough}**	**C_{max}**	**AUC**	**C_{trough}**
[†]Cabotegravir (30 mg single oral)	3.61 (3.28-3.96)	146 (128-167)	[§]1.72	3.15 (2.99-3.31)	99 (94-103)	1.51 (1.44-1.59)	-12.8	-32.2	-12.2
[‡]Cabotegravir (800 mg IM, 84 days)[2]	3.3 (59)	4467 (52)	1.1 (140)	3.5 (21)	5166 (23)	1.2 (24)	6.1	15.6	9.1

Cabotegravir C_{max} and C_{trough} are in µg/ml, AUC in µg.h/ml.
[†]Cabotegravir values are for a single oral dose, values are expressed in geometric least-squares mean (range).
[§]Cabotegravir C_{trough} was obtained from digitalised plots and not provided in the reference, hence standard deviation was not included.
[‡]Values are represented as geometric mean (% CV – coefficient of variation expressed as a percentage). The intramuscular administrations were subsequent to 28 days of oral cabotegravir (30 mg OD).

[1]Ford, S.L., et al. Antimicrobial Agents and Chemotherapy, 2017. **61**(10).
[2]Spreen, W., et al. Journal of Acquired Immune Deficiency Syndromes, 2014. **67**(5): p. 487-492.

Norelgestromin PBPK qualification

- A proportional release rate of 3×10^{-3}, 4.5×10^{-3} & 6×10^{-3} h^{-1} were considered, given the patch sizes of 10 cm^2, 15 cm^2 and 20 cm^2 respectively

Table Pharmacokinetic comparison of norelgestromin following single application of different patch sizes

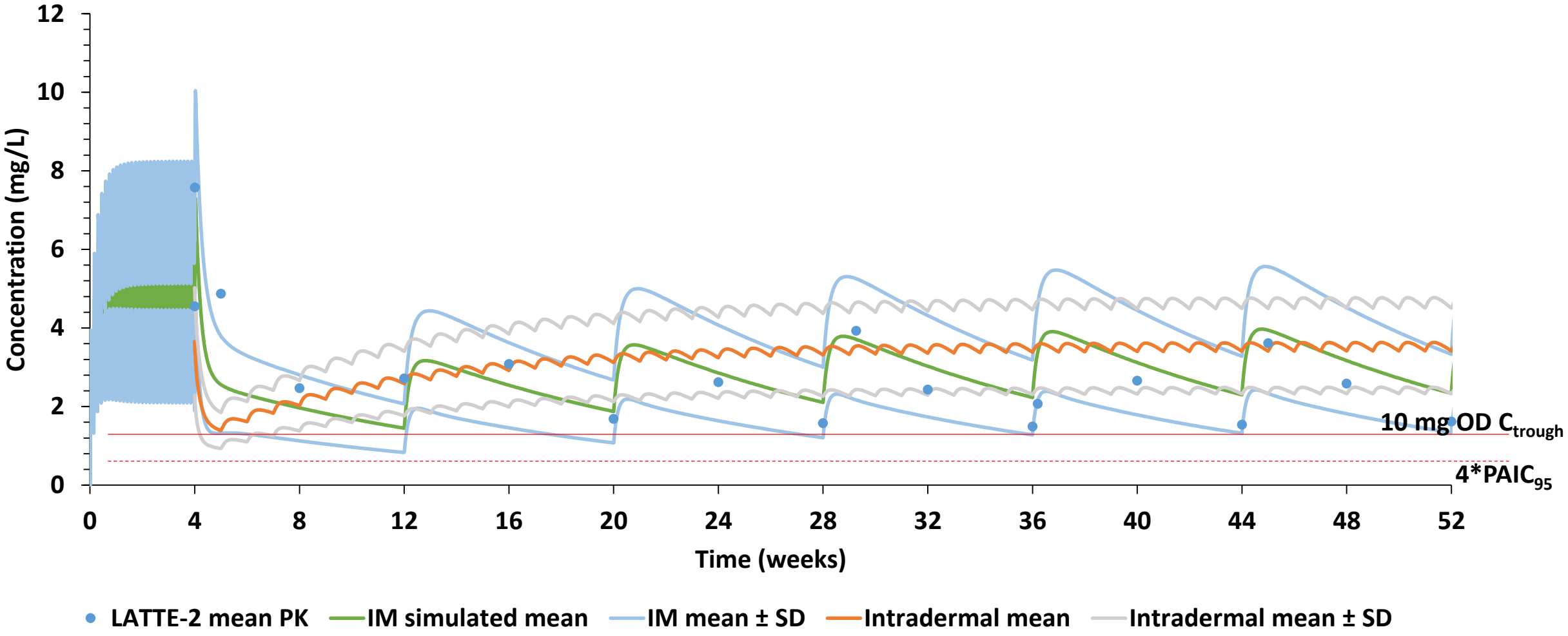
Patch size →	Clinical[1]			Simulated			% difference		
	10 cm^2	15 cm^2	20 cm^2	10 cm^2	15 cm^2	20 cm^2	10 cm^2	15 cm^2	20 cm^2
C_{ss}	0.46 ± 0.16	0.62 ± 0.21	0.83 ± 0.21	0.59 ± 0.21	0.76 ± 0.27	1.12 ± 0.39	28.3	22.6	34.9
$AUC_{0\text{-}168h}$	68.8 ± 24.1	92.5 ± 33.2	123 ± 32.3	84.3 ± 26.9	108 ± 36.5	161 ± 53.4	22.5	16.8	30.9
$AUC_{0\text{-}240h}$	81.2 ± 27.7	110 ± 37.9	146 ± 37.9	98.1 ± 31.8	126 ± 41.9	185 ± 62.1	20.8	14.5	26.7

Values are represented as mean ± SD. C_{ss} – steady state concentration represented in ng/ml, AUC is represented in ng.h/ml

[1] Larry S. Abrams et al. Fertility and Sterility. 2002;77(2), Suppl 2:S3-S12

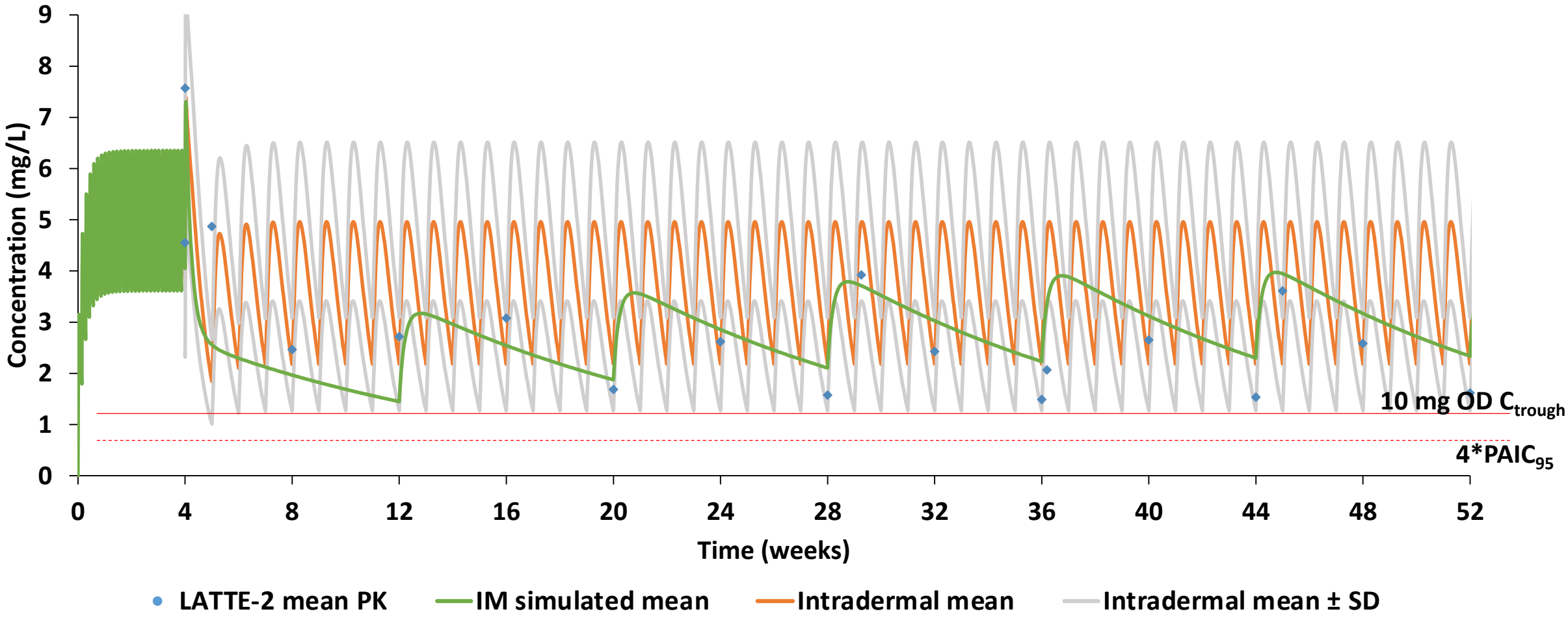
CAB IM bimonthly vs MAP weekly

IM simulated (Q8w) 800 mg LD, 600 mg MD (7.6×10^{-4} h^{-1}) vs. MAP 300 mg LD, 90 mg MD weekly (7.6×10^{-4} h^{-1}, same as IM)



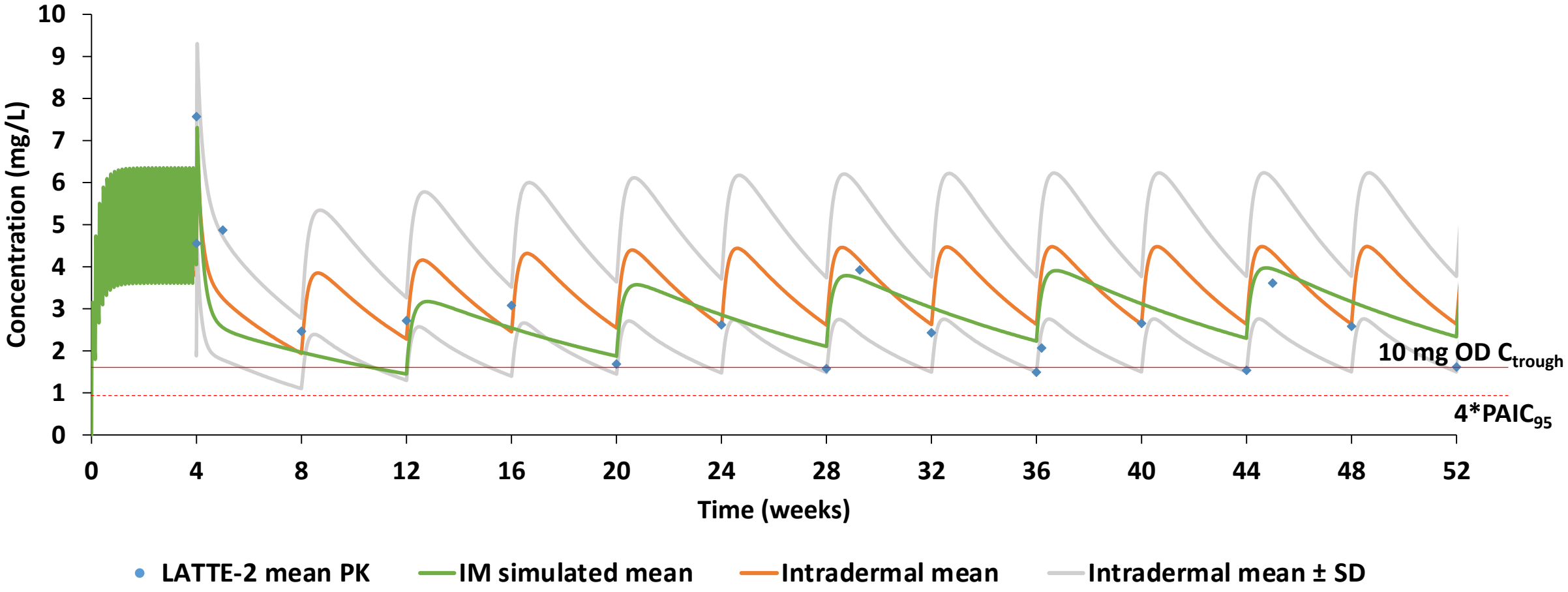
CAB IM bimonthly vs MAP weekly

IM simulated (Q8w) 800 mg LD, 600 mg MD (7.6×10^{-4} h^{-1}) vs. MAP 90 mg LD (Qw), 90 mg MD (Qw) (1×10^{-2} h^{-1})

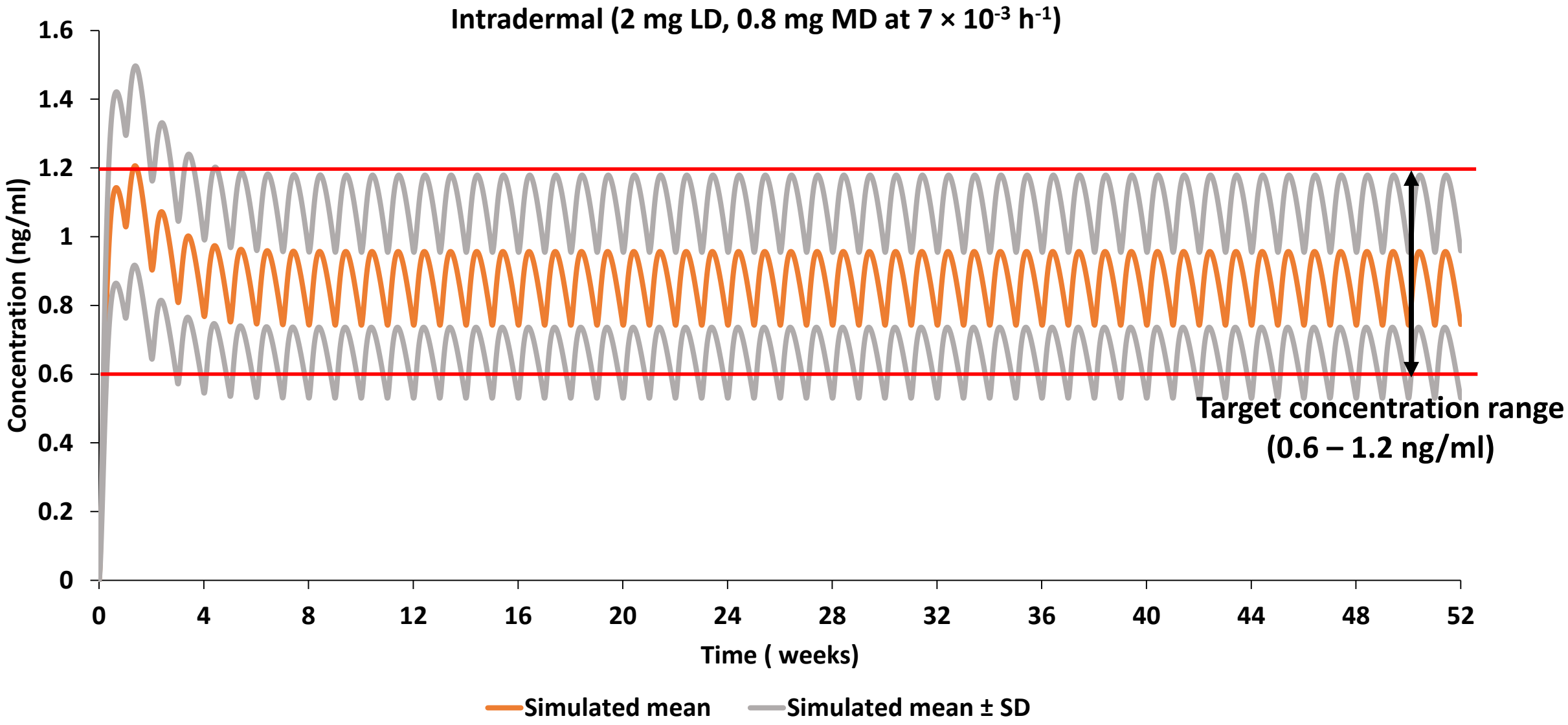


CAB IM bimonthly vs MAP monthly

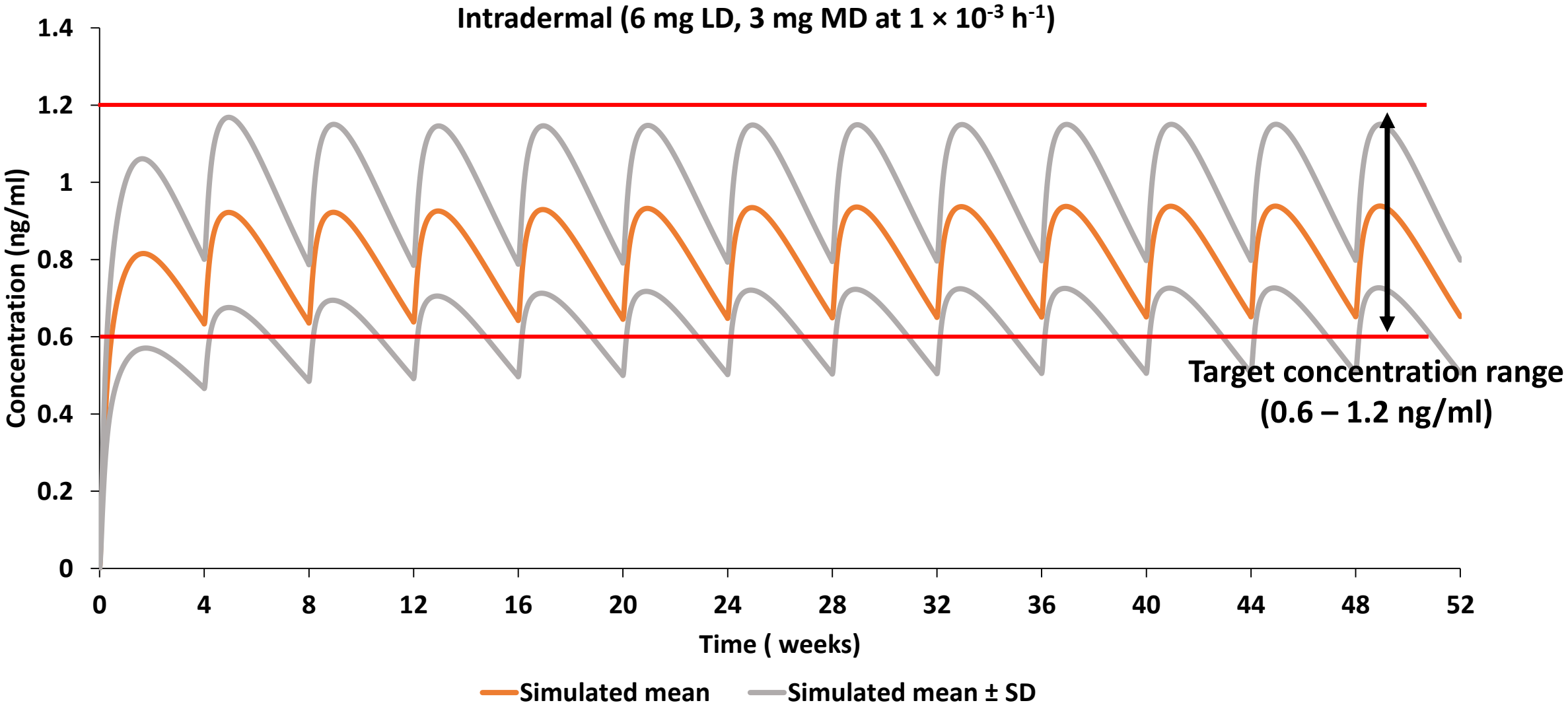
IM simulated (Q8w) 800 mg LD, 600 mg MD (7.6×10^{-4} h^{-1}) vs. MAP 540 mg LD (Q4w), 360 mg MD (Q4w) (1×10^{-3} h^{-1})



Norelgestromin intradermal weekly



Norelgestromin intradermal monthly



Results summary

- Higher loading dose is necessary for CAB formulation with release rate equivalent to the IM injection
- Longer time to reach steady state levels (≈40 weeks) is observed for formulation with IM release rate
- Loading dose at least double that of the maintenance dose is necessary for NGMN long-acting MAPs
- A 12 × 12 cm size patch would be needed for 540 mg dose of cabotegravir

Limitations

- Physiological changes at the administration site could affect the release
- Long-term drug and excipients stability at the site of application represent a key factor
- Developed model assumes 100% bioavailability, however low bioavailability will require higher dose and a larger MAP
- Further qualification against intradermal PK from pre-clinical and human data would improve the confidence of the PBPK model

Conclusions

- Intradermal delivery represents an attractive, minimally invasive and effective route for long-acting administration
- Combination of CAB and NGMN weekly and monthly intradermal MAPs have rational patch sizes
- PBPK modelling can be used to predict formulation characteristics needed to achieve target concentrations for novel ARV/contraceptive combination devices

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