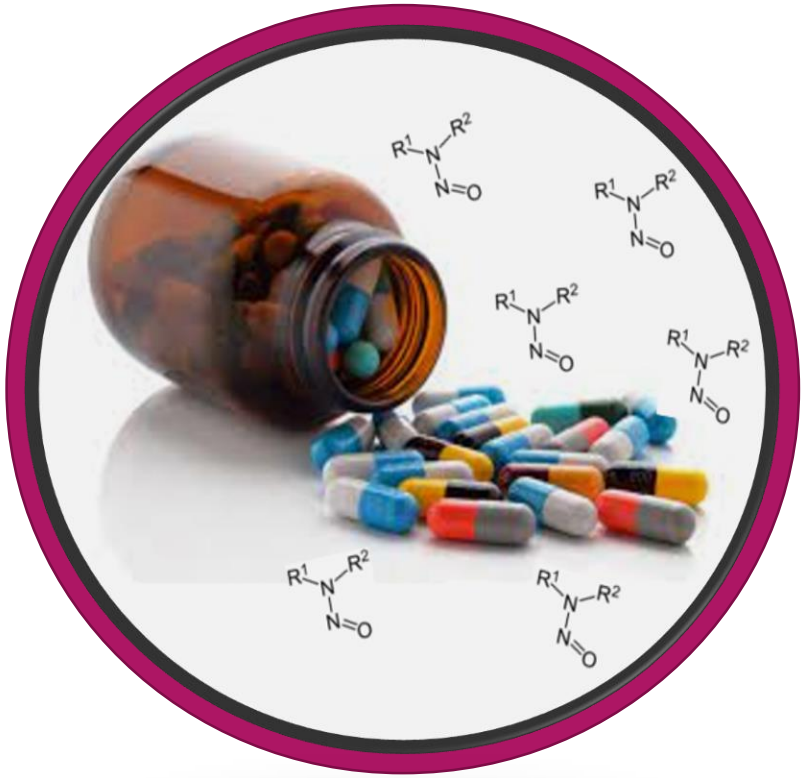
Alternatives for Rifampin as a CYP3A Inducer in DDI Studies in View of N-Nitrosamine Impurity Issues



Aernout van Haarst PhD & Sabina Paglialunga PhD
Directors Scientific Affairs, Celerion

14 June 2023

Everyone is Exposed to Some Level of Nitrosamines

Cured and Grilled Meats

Vegetables

Dairy Products

Drinking Water

Cosmetics

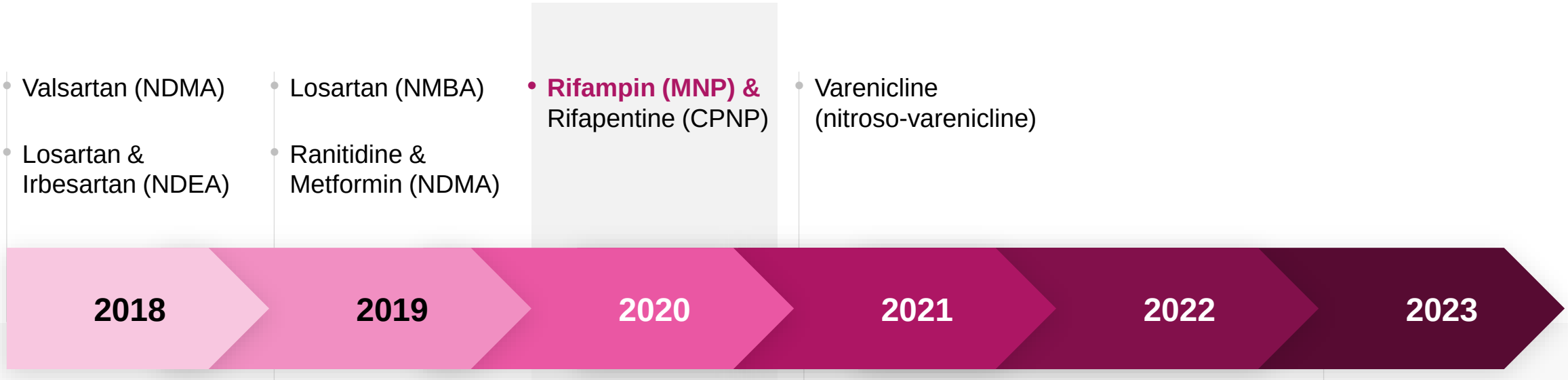
Drugs

Detergents and Solvents

Plastic and Chemicals

Tobacco

Nitrosamine Impurity Chronology in Marketed Medication



	2018	2019	2020	2021	2022	2023
	Valsartan (NDMA) Losartan & Irbesartan (NDEA)	Losartan (NMBA) Ranitidine & Metformin (NDMA)	**Rifampin (MNP) &** Rifapentine (CPNP)	Varenicline (nitroso-varenicline)		
Regulatory Response:		**EMA Scientific Opinion** September	**EMA Guidelines** June **FDA Guidance** September	**Risk Assessment Step 1** March **FDA Guidance** February		**Risk Assessment Step 2 & 3** October **FDA Workshop** May/June

CPNP, 1-cyclopentyl-4-nitrosopiperazine; **NMBA**, N-nitroso-N-methyl-4-aminobutyric acid; **NDEA**, N-Nitrosoethylisopropylamine; **MNP**, 1-methyl-4-nitrosopiperazine

What are N-Nitrosamines?

Probable or possible human carcinogens

- Chemical compounds with a functional N-nitroso group (>N-N=O)
- Nitrosamines are metabolized in the liver (CYP2E1) and can produce DNA reacting agents
  - Cytotoxic
  - Mutagenic
  - Carcinogenic
- ICH M7: Cohort of concern
- Small alkyl compounds (e.g. rifampin impurity, MNP)
- API-derived complexes called **N**itrosamine **D**rug **S**ubstance **R**elated **I**mpurities (**NDSRIs**) (e.g. nitroso-varenicline)
  - Derived from nitrosation of secondary or tertiary amines in drug structure

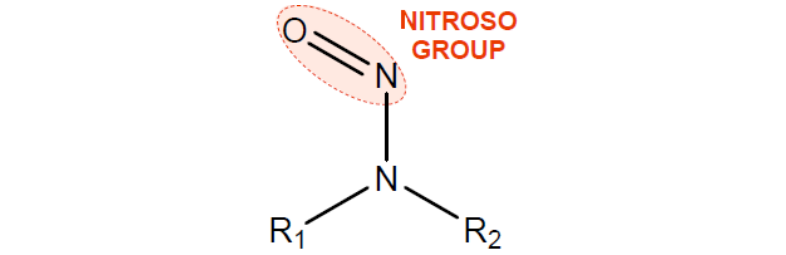
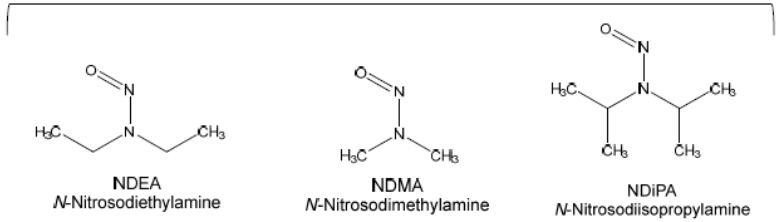


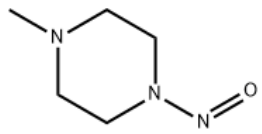
Figure 1. Generic *N*-nitrosamine structure



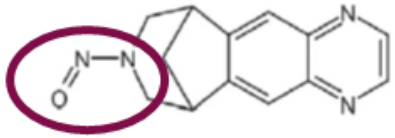
NDEA
N-Nitrosodiethylamine

NDMA
N-Nitrosodimethylamine

NDiPA
N-Nitrosodiisopropylamine



MNP
1-methyl-4-nitrosopiperazine
Rifampin Impurity

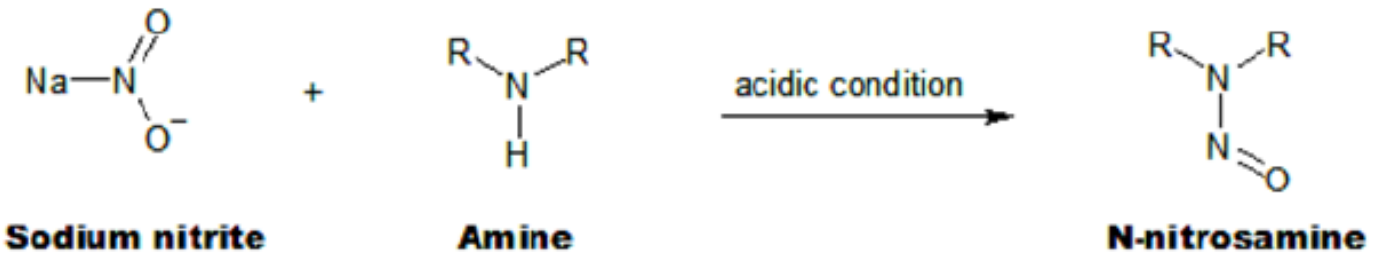


Nitroso-varencicline
NDRSI

Schlingemann et al. J Pharm Sci 2022.

Nitrosamine Source in Marketed Drug

During drug manufacturing, nitrosamines can be formed from reactions of secondary amines with nitrite in acidic conditions.



During Manufacturing

- Nitrites – applied to quench azide reactions
- Sodium nitrate and sodium azide impurities with sodium nitrites
- Organic nitrites converted to inorganic nitrites
- Water
- Solvents
- Amines in chemical synthesis, or formed during a reaction

Post Manufacturing

- Interaction with excipients
- Packaging – blister pack ink may contain amines
- Degradation products

Schlingemann et al. J Pharm Sci 2022.

Regulatory Guidance to Control N-Nitrosamine Impurities

March 31st, 2021

Step 1: Risk assessment

October 1st, 2023

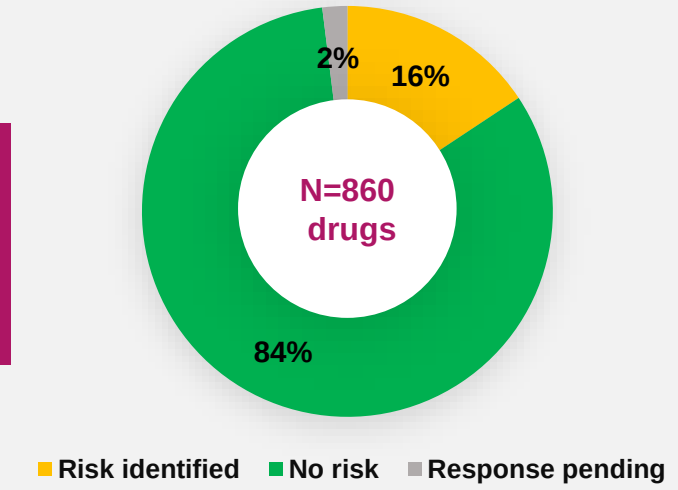
Step 2: Confirmatory testing if risks are identified

Step 3: Reporting changes implemented to prevent or reduce the presence of nitrosamine impurities in drug products in approved and pending NDAs and ANDAs

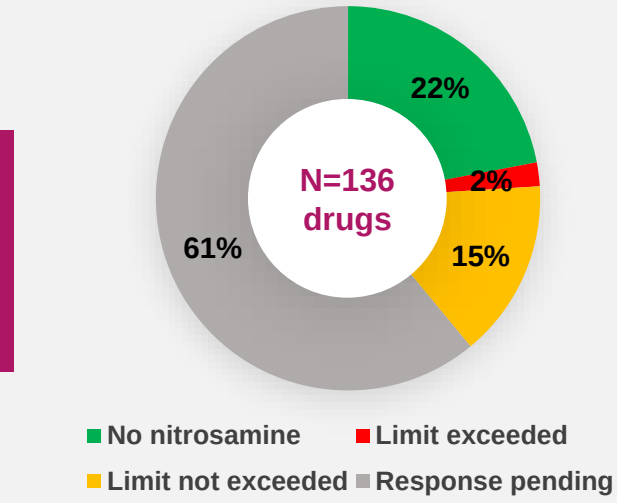
- **EMA Assessment Report:** Nitrosamine Impurities in Human Medicinal Products, June 2020 www.ema.europa.eu/en/human-regulatory/post-authorisation/referral-procedures/nitrosamine-impurities
- **FDA Guidance for Industry:** Control of Nitrosamine Impurities in Human Drugs, February 2021 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/control-nitrosamine-impurities-human-drugs

Graphs redrawn from:
https://www.ema.europa.eu/en/documents/presentation/presentation-update-activities-linked-presence-n-nitrosamines-human-medicines-mfilancia-ema_en.pdf

Step 1



Step 2



DDI Substrates and Perpetrators: Impurities Reported

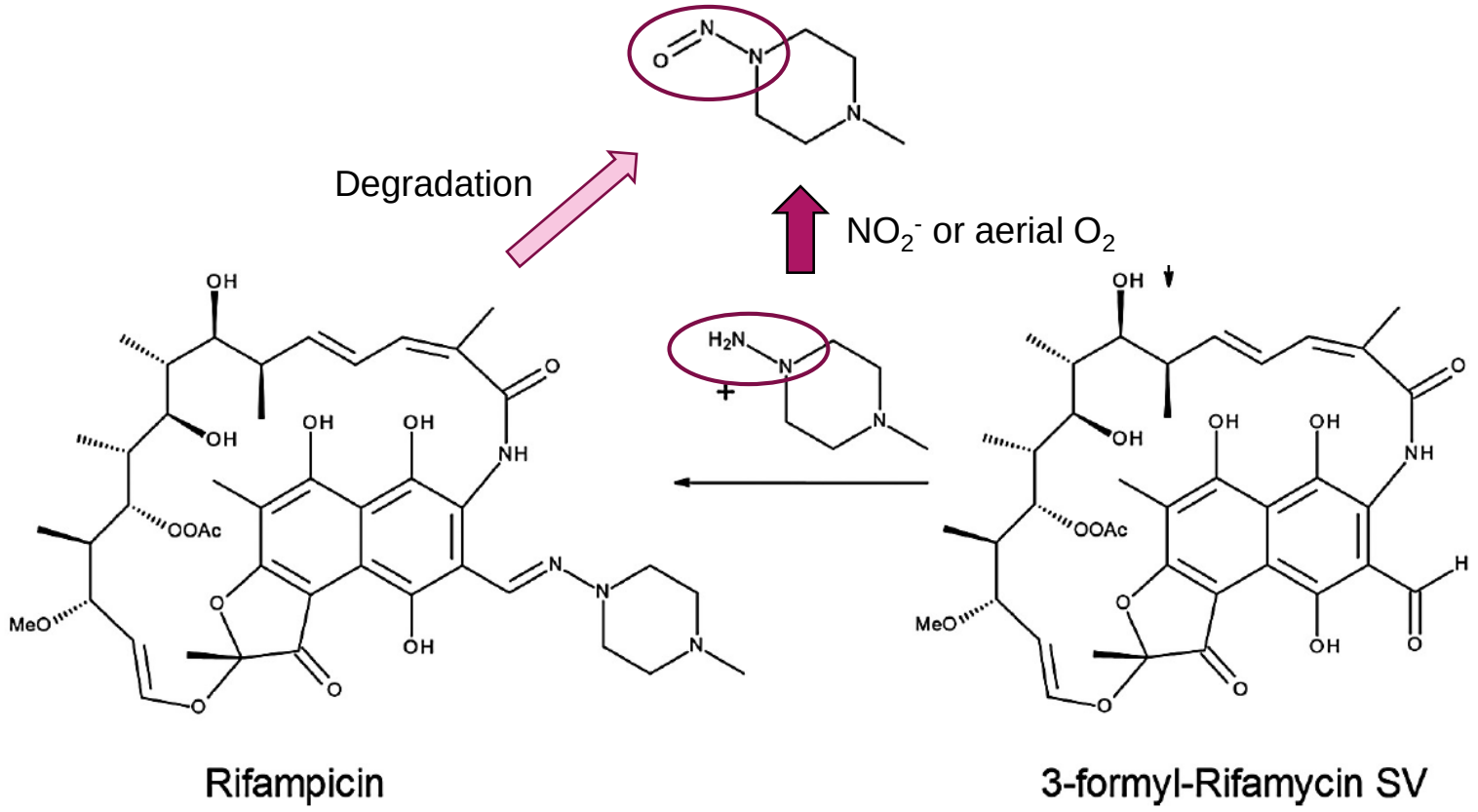
Drug	Nitrosamine Detected	Role in DDI Studies	Impact to DDI Studies	Alternatives for DDI Studies
Ranitidine, Nizatidine	NDMA	Acid reducing agent	Removed from market (ranitidine) or recalled (nizatidine)	Famotidine or proton pump inhibitor (esomeprazole or rabeprazole)
Metformin	NDMA	OCT2, MATE1/2K substrate	No impact	IR-metformin is available for DDI studies and does not contain impurity
Rifampin	MNP	1. Strong CYP3A4 inducer 2. OATP1B1/3 inhibitor (single dose)	Batches available for patients only, use alternatives	1. Carbamazepine, efavirenz, lumacaftor, phenytoin 2. Atazanavir & ritonavir, clarithromycin, cyclosporine, gemfibrozil, lopinavir, ritonavir
Propranolol	nitroso-propranolol	CYP2D6 substrate	Product recalled (CND), but no impact (not an index substrate)	Desipramine, dextromethorphan, nebivolol

Paglialunga & van Haarst. J Pharm Sci 2023.

N-Nitrosamine Source - Manufacturing Risk

- Rifampin is derived from rifamycin B and is used for treating tuberculosis (TB)
- During manufacturing, addition of AMP can lead to MNP formation
- Thermal degradation may also increase MNP levels

N-nitrosamine: MNP = 1-methyl-4-nitrosopiperazine



AMP = 1-amino-4-methilpiperazine

Wohlfart et al. J Pharma Biomed Analysis 2021.

Acceptable Intake (AI) Limits

- AI limit is a daily exposure to a compound that approximates a 1:100,000 cancer risk after 70 years of exposure
- Derived from nonclinical TD_{50}
- MNP TD_{50} values not considered reliable
  - NDMA applied as a surrogate
- Conversion to parts per million (ppm) is product-dependent and calculated based on a drug's max daily dose

Nitrosamine	AI Limit (ng/day)[1]
NDMA	96
NDEA	26.5
NMBA	96
NMPA	26.5
NIPEA	26.5
NDIPA	26.5
MNP	96 (NDMA surrogate value)

Calculating MNP AI for Rifampin:

- Rifampin daily dose = 600 mg/day
- MNP ppm = 96 ng/day / 600 mg/day **= 0.16 ppm**

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/control-nitrosamine-impurities-human-drugs

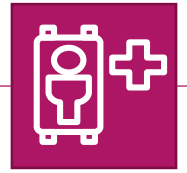
MNP Levels in Rifampin

Company (Manufacturer)	Product	MNP level (ppm)[1]	Status[2]
Akorn	Rx Rifampin 300 mg	1.49-3.20	Discontinuation of manufacture of drug (Sep 2022) Filed for bankruptcy (2023)[3]
Akorn	Rx Rifampin 150 mg	2.95-3.47	
Fresenius Kabi	Rx Rifampin Injection 600 mg	0.94	Available (Mar 2023)
Lannett	Rx Rifampin 300 mg	1.88-2.52	
Lannett	Rx Rifampin 150 mg	2.22-2.43	
Lupin Pharmaceuticals Inc.	Rx Rifampin 300mg	1.31-2.08	Available (Mar 2023)
Lupin Pharmaceuticals Inc.	Rx Rifampin 150mg	1.52-2.26	
Mylan	Rx Rifampin Injection 600 mg	0.99-2.51	Unavailable (Mar 2023)
Sandoz/Epic	Rx Rifampin 300 mg	1.86-2.66	Available (Jan 2023)
Sandoz/Epic	Rx Rifampin 150 mg	2.39-2.76	
Sanofi Pharmaceuticals	Rx Rifampin Injection 600 mg	0.80-1.11	Available (Jun 2021)

1. https://www.fda.gov/drugs/drug-safety-and-availability/laboratory-analysis-rifampinrifapentine-products
2. https://www.accessdata.fda.gov/scripts/drugshortages/dsp_SearchResults.cfm
3. https://eu.usatoday.com/story/money/2023/05/01/akorn-drug-recall/11761785002

Temporary AI Limits for Patients

> The acceptable intake limits are 0.16 parts per million (ppm) for MNP in rifampin and 0.1 ppm for CPNP in rifapentine. The agency ***will not object*** to certain manufacturers ***temporarily*** distributing rifampin containing ***MNP below 5 parts per million (ppm)***. The agency also will not object to certain manufacturers temporarily distributing rifapentine containing CPNP below 14 ppm. FDA will not object to these higher exposures to ***maintain patient access*** to these life-saving medications.



Risk of not treating TB outweighs theoretical risk of cancer

https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-nitrosamines-rifampin-and-rifapentine

Rifampin Use in Healthy Volunteers; Regulatory Positions

FDA:
Per Celerion-Sponsor communication:

FDA notified 2 of our Sponsors that ***using rifampin in healthy subjects is NOT acceptable*** and suggested to one of the sponsors to use phenytoin or carbamazepine

EMA:
Per EMA Committee for medicinal products for human use – Meeting minutes 19-22 Apr 2021:

The CHMP noted the question from the PKWP on the ***use of Rifampicin in Drug Interaction Studies in healthy volunteers*** and discussed the recommendation from the Nitrosamine Implementation Oversight Group (NIOG) that ***Rifampicin containing nitrosamine above the acceptable intake should not be used*** in these studies. The CHMPI was in agreement with the recommendation and adopted the response to PKWP.

MHRA:
Per general Celerion inquire to MHRA:

The Commission on Human Medicines has advised that that rifampicin should, at present, ***not be used in Drug-Drug-Interaction studies healthy volunteers***. Alternative suitable PK-inducers, such as Rifabutin, may be used instead.

Alternative CYP3A Inducers for DDI Studies

Rifampin Replacement Candidates

Perpetrator	Drug Type & Indication	Comments	Suitable?
Apalutamide	Nonsteroidal antiandrogen	Increased risk of seizure and incidence of fall and fractures	✗
Carbamazepine	Sodium channel blocker	Dose titration to mitigate AEs and black box warning	✓
Efavirenz	Nonnucleoside rt inhibitor	Listed in ICH M12 Guidance; only moderate inducer	?
Enzalutamide	Nonsteroidal antiandrogen	Increased risk of seizure and incidence of fall and fractures	✗
Ivosidenib	Mutant isocitrate-DH1 inhibitor	Multiple doses of ivosidenib not studied in healthy participants (lack of data)	✗
Lumacaftor	CFTR modulator	Only in combination with ivacaftor (Orkambi). Favorable safety profile	?
Mitotane	Adrenal cytotoxic agent	Occurrence of common AEs >15%	✗
Phenytoin	Sodium channel blocker	Narrow therapeutic window, yet preferred perpetrator	✓ ✓
Rifabutin	Antimicrobial	MHRA recommendation; not an option listed by FDA	✗
St. John's wort	Herbal supplement	Effect varies widely and is preparation-dependent	✗

Adapted from FDA Drug-Drug Interactions Table 3.3
www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers.

Carbamazepine as Alternative?

- Anticonvulsant drug
- **Strong inducer of CYP3A** (via CAR/PXR);
  - Also strong inducer of CYP2B6
  - Weak inducer of CYP2C9
  - Inducer of P-gp
- **Safety concerns:**
  - Risk of **severe cutaneous adverse reactions** with high starting doses (**Black Box warning**)
  - Risk of aplastic anemia & agranulocytosis
- Risk mitigation measures
  - Exclude anyone with positive HLAB*1502 allele (~ risk of CBZ hypersensitivity reactions)
  - Dose titration to mitigate AEs
    - 3+3 days 100 / 200 mg BID; ≥7 days 300 mg BID
  - Monitor platelet and WBC counts

- Sufficient experience with DDI trials in healthy volunteers

> In study A, 7 out of twelve subjects completed the study according to protocol. Five subjects discontinued the study due to the emergence of generalized exanthema, a well-known and common side effect of carbamazepine. In three

Sitsen et al., Eur. J. Drug Metab. Pharmacokinet. 2001.

Paglialunga & van Haarst. J Pharm Sci 2023.

Phenytoin as Alternative?

- Anticonvulsant drug
- **Strong inducer of CYP3A** (via CAR/PXR)
  - Also moderate inducer of CYP1A2 and CYP2C19
  - Inducer of P-gp
- **Narrow therapeutic window**
  - Safety concerns (e.g. risk of seizures & neurological events)
- Sufficient experience with DDI trials in healthy volunteers

- **Long half-life,** requiring time to reach Css and maximal CYP3A induction
- Risk mitigation measures
  - Genotyping CYP2C9 and CYP2C19 poor metabolizers
  - Exclude history of seizures, neurological conditions and suicide ideation
  - Exclude WCBP because of prenatal risks
  - If substrate may increase phenytoin levels, monitor phenytoin levels
- Recommended phenytoin regimen: 100 mg TID phenytoin for ≥14 days

Paglialunga & van Haarst. J Pharm Sci 2023.

Phenytoin Safety Profile

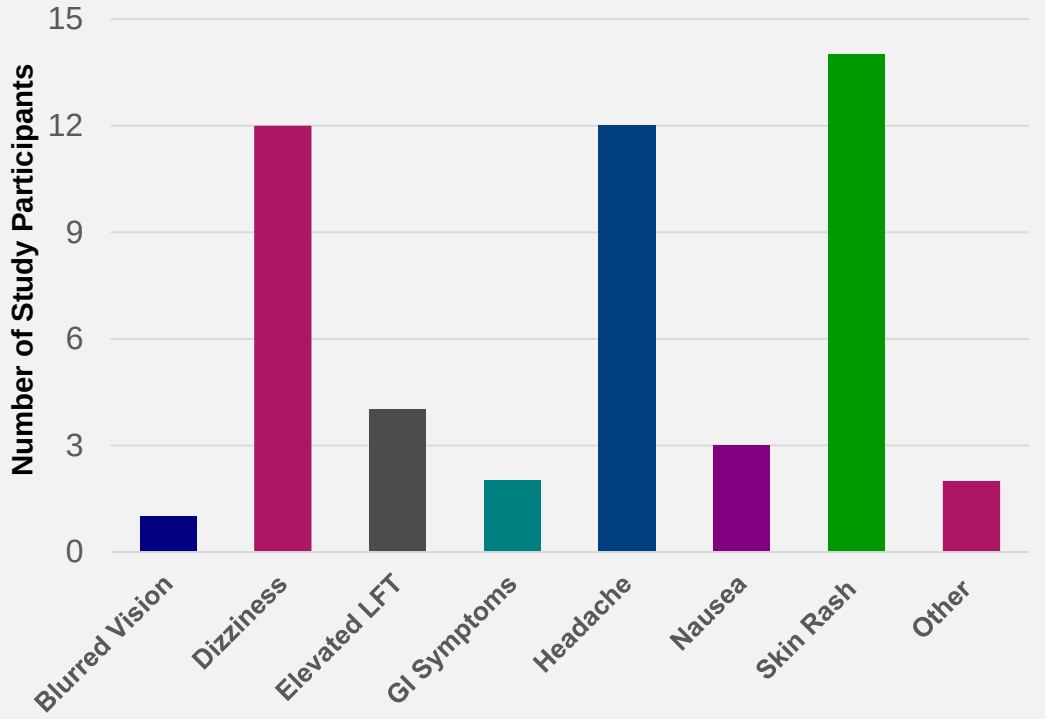
Literature phenytoin DDI studies:

- 16 studies published
- AEs were mild to moderate and transient in nature
- Most common AEs:
  - Skin rash, Dizziness, Headache

Celerion phenytoin DDI experience:

- 8 DDI studies in past 2 yrs
- PHT generally well tolerated
- No dropouts due to phenytoin AEs

Phenytoin-Related AEs from Published DDI Studies

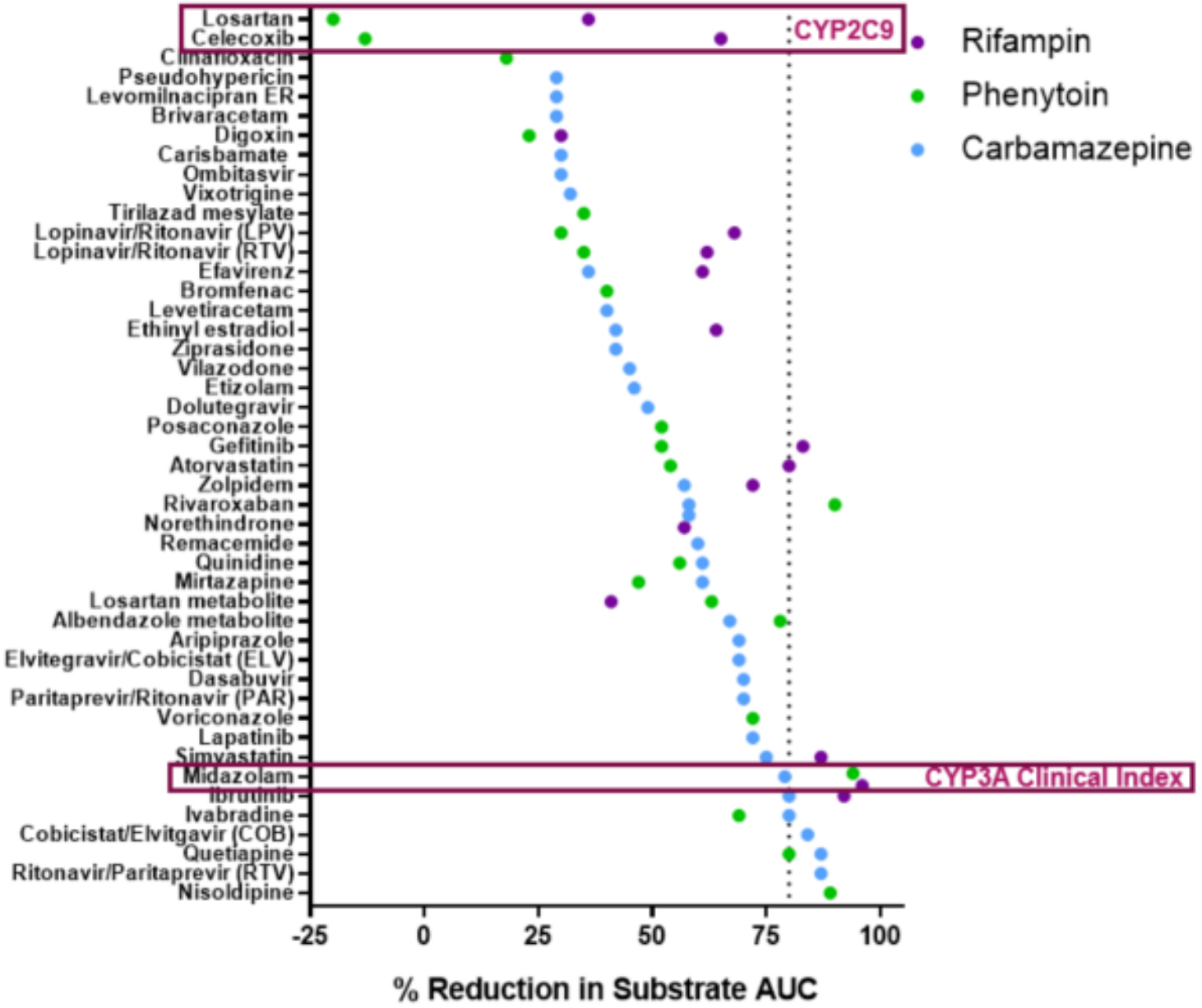


Paglialunga & van Haarst, 2022 ACCP Poster Presentation.

Strong CYP3A Inducers

- Literature review
- Spectrum of substrate reduction in the presence of strong CYP3A inducers
- Overall **phenytoin** and **carbamazepine** induce a similar %AUC reduction as **rifampin**

Paglialunga & van Haarst, 2022 ACCP Poster Presentation.



Case Studies:
PHT and CBZ DDI Studies

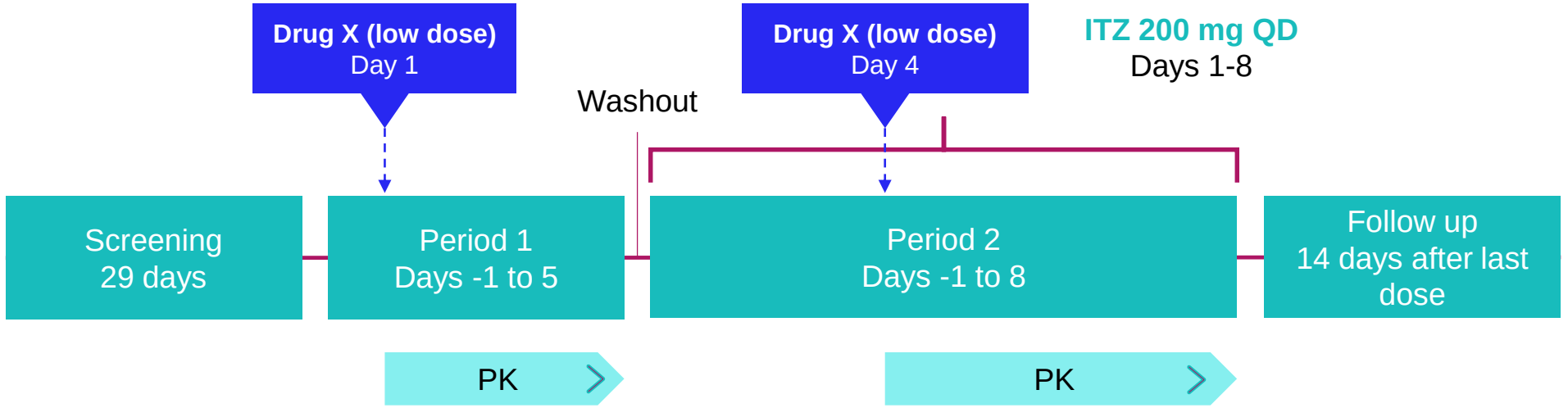
Case Study 1 – Phenytoin-Induced CYP3A Activity

DDI study to determine the effect of itraconazole (ITZ) and phenytoin (PHT) on the single dose PK of Drug X

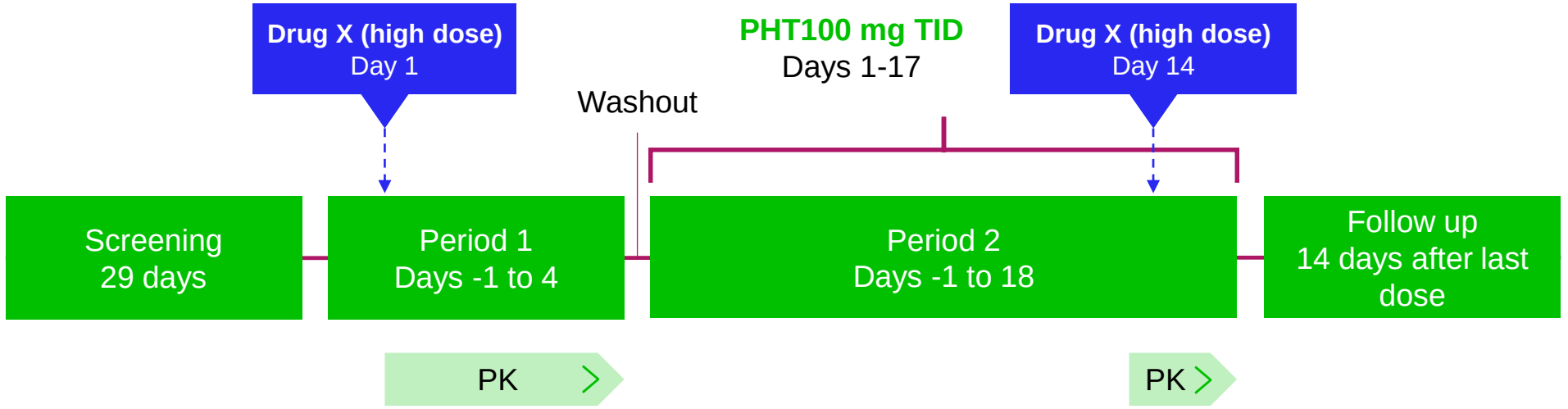
- Drug X is being developed to treat cancer
- Nonclinical data suggests Drug X is a CYP3A substrate
- ITZ is a strong CYP3A4 and P-gp inhibitor
- PHT is a strong CYP3A4 inducer
- 2 Dose levels applied for Drug X:
  - ITZ arm: Low dose Drug X to avoid over-exposure with decreased clearance
  - PHT arm: High dose Drug X for more accurate PK parameters
- 6β-hydroxycortisol / free cortisol as CYP3A endogenous induction biomarker
- Part 2: CYP2C9 and CYP2C19 poor metabolizers excluded

Case Study 1 – Study Design

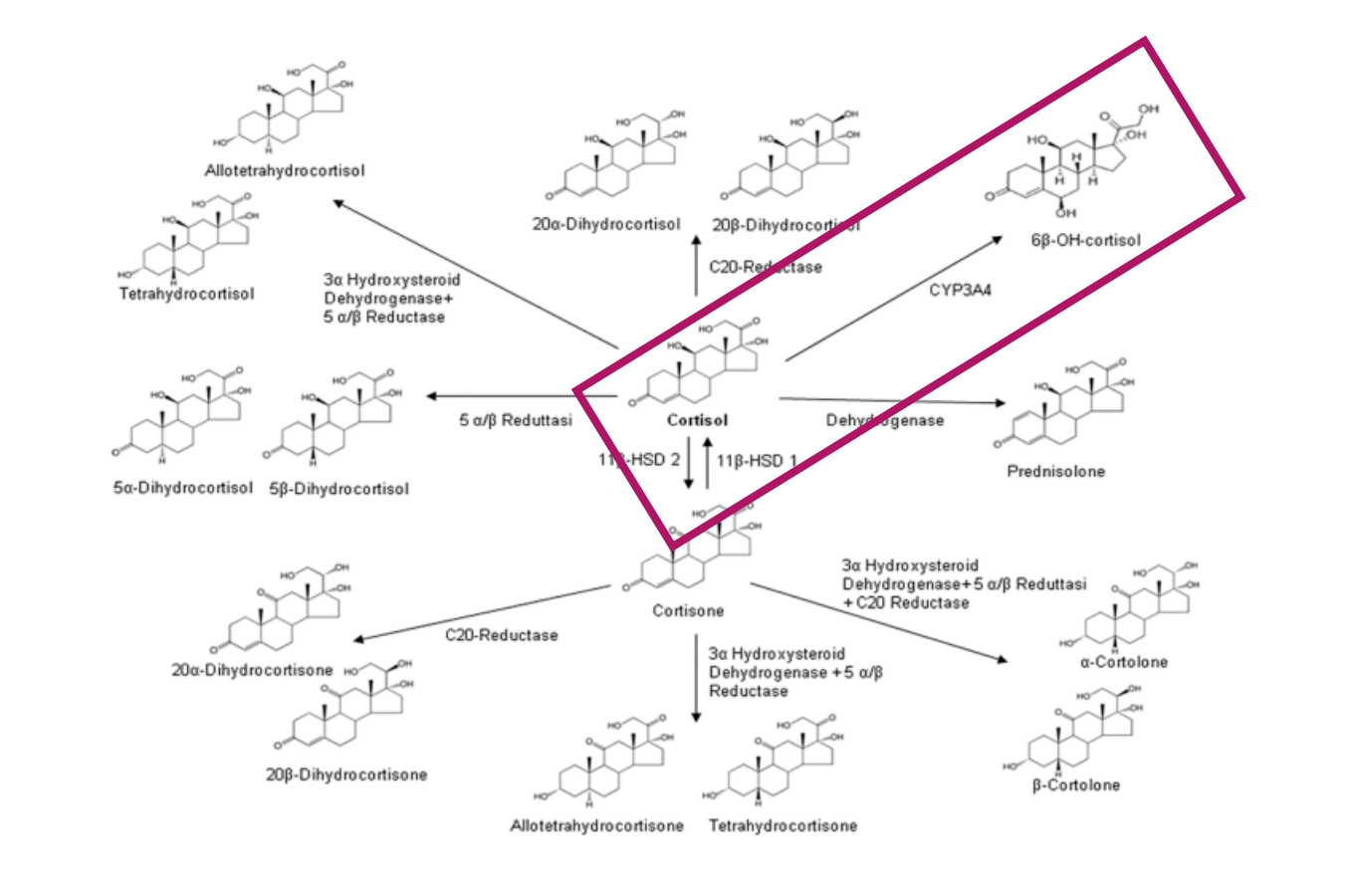
Part 1
(ITZ)

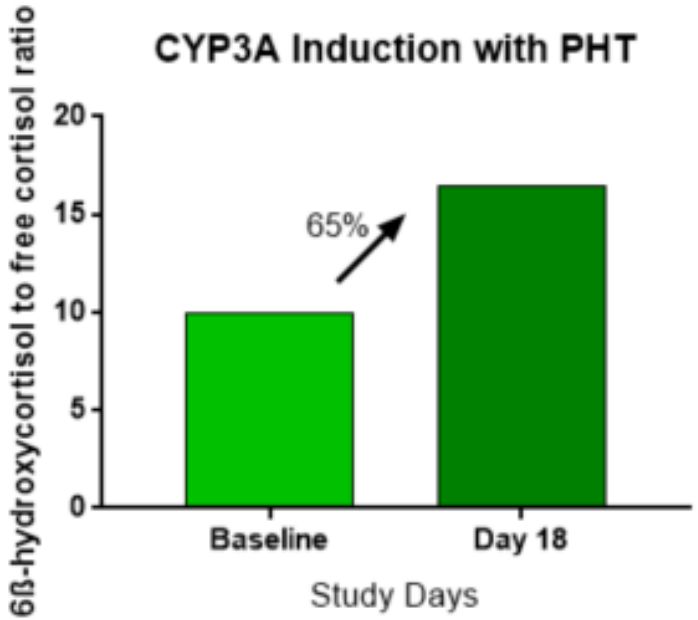


Part 2
(PHT)



Case Study 1 - Strong CYP3A Induction with PHT





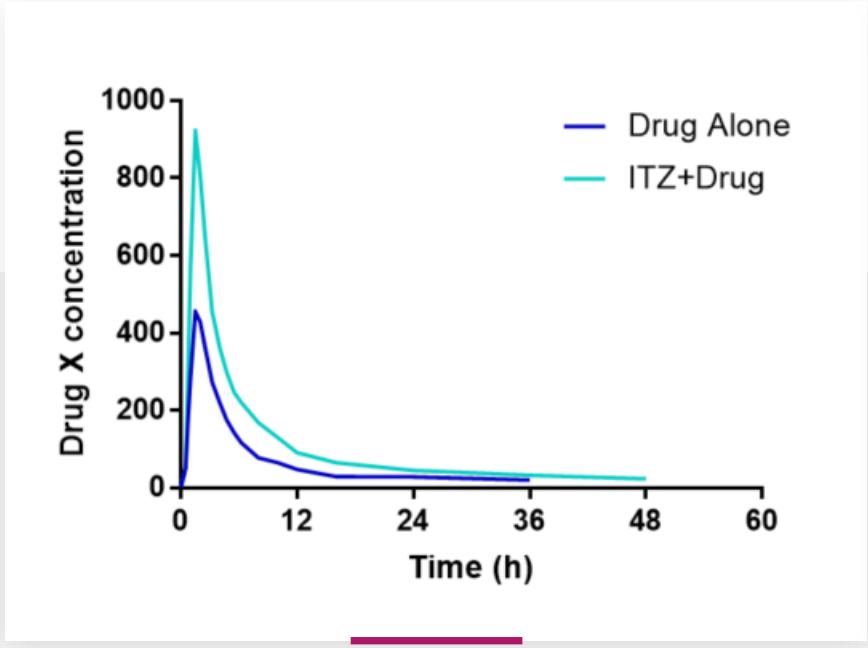
Arioli, F. et al. Anal Bioanal Chem 2022.

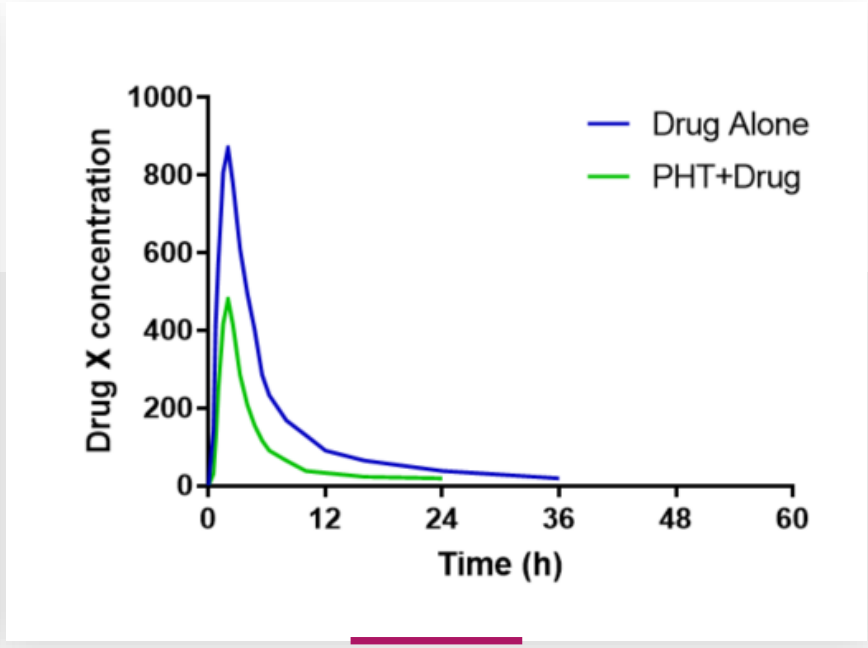
Case Study 1 - Moderate Induction and Inhibition Effects on Drug X

ITZ co-administration
- Moderately increased exposure of Drug X

PHT co-administration:
- Induced a robust CYP3A induction *(confirmed by endogenous biomarker)*
- Moderately reduced exposure of Drug X

Co-administration with strong CYP3A inhibitors and inducers has risks





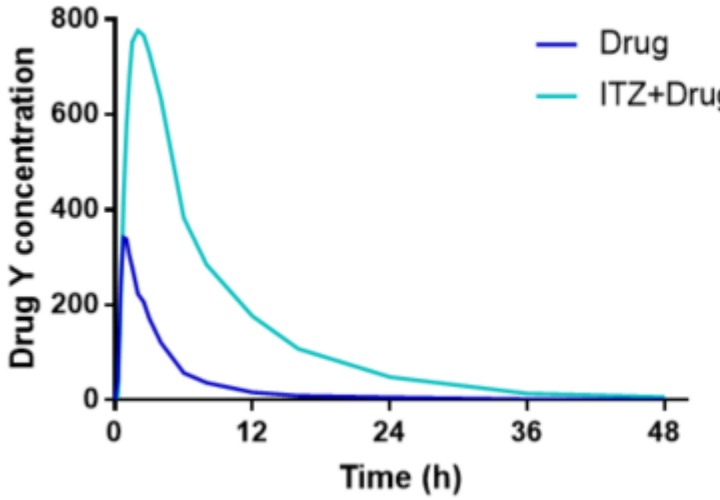
PK Parameter	ITZ+Drug	PHT+Drug
Dose	Low dose	High dose
Cmax	↑ 95%	↓ 50%
$AUC_{0\text{-inf}}$	↑105%	↓ 60%

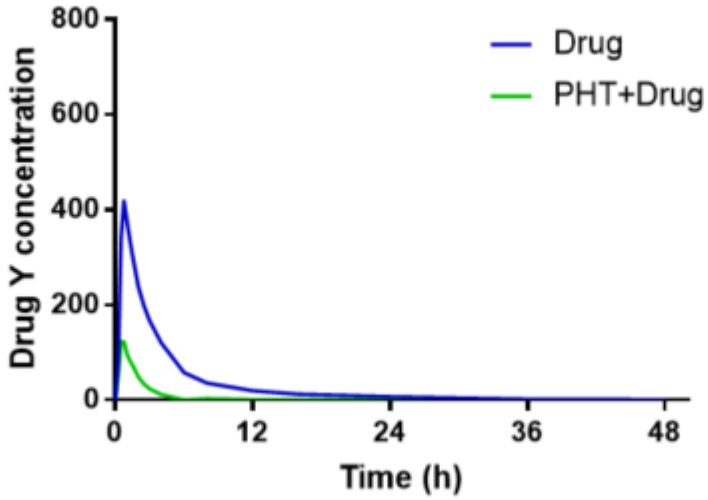
Case Study 2 – CYP3A & P-gp

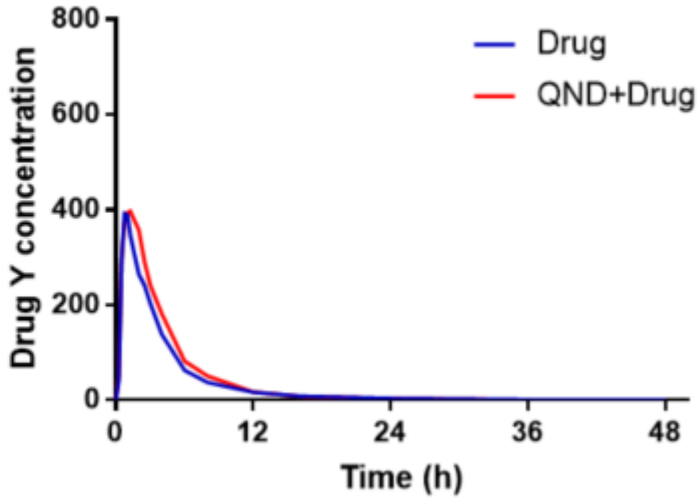
DDI study to determine the effect of CYP3A and P-gp inhibition and induction on the single dose PK of Drug Y

- Drug Y is being developed for treatment of cardiovascular disease
- Nonclinical data suggests Drug Y is a CYP3A and P-gp substrate
- ITZ is a strong CYP3A4 & clinical P-gp inhibitor
- PHT is a strong CYP3A4 inducer & P-gp inducer
- Quinidine (QND) is a clinical P-gp inhibitor
- Part 2: CYP2C9 and CYP2C19 poor metabolizers excluded
- 3-part, open-label, fixed sequence, 2 periods
  - Part 1: Period 1 – Drug Y alone; Period 2 – ITZ 200 mg QD (Days 1-6) co-admin with Drug Y (Day 5)
  - Part 2: Period 1 – Drug Y alone; Period 2 – PHT 100 mg TID (Days 1-15) with co-admin with Drug Y (Day 14)
  - Part 3: Period 1 – Drug Y alone; Period 2 – QND 300 mg (Day 1, t=-1h & 3h), Drug Y (Day 1, t=0h)

Case Study 2 – Dynamic CYP3A Activity, no P-gp Effect







PK Parameter	ITZ+Drug Y	PHT+Drug Y	QND+Drug Y
Cmax	↑ 135% (**+1.35-fold change**)	↓ 65% (**-2.8-fold change**)	↑ 15%
$AUC_{0\text{-inf}}$	↑ 420% (**+4.2-fold change**)	↓ 80% (**-5-fold change**)	↑ 20%

- Similar (but inverse) dynamic change with strong CYP3A inhibitor and inducer
- Minimal P-pg contribution as demonstrated by QND effect
- Co-administration with strong CYP3A inhibitors and inducers may need to be avoided

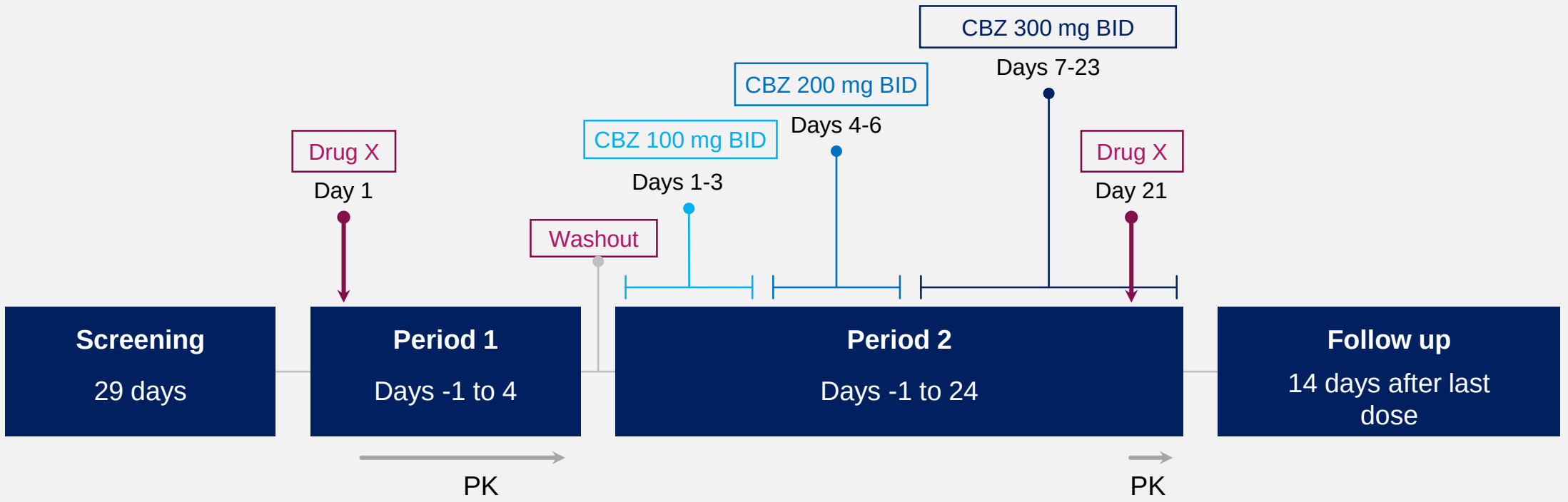
Adverse Event (AE) Frequency from Phenytoin Case Studies

AE Frequency:	n = 1	n = 2-5	n > 5
Case Study 1	• Blurred Vision • Fatigue • GI Symptoms • Nausea	• Dizziness • Elevated LFT • Headache • Other	• Skin Rash
Case Study 2	• Nausea	• Fatigue • GI Symptoms • Skin Rash	• Headache

All AEs were mild to moderate and transient in nature

Typical Carbamazepine DDI Study Design

Dose Titration:



Adapted from Bolledula et al, Clin Transl Sci. 2022.

Case Study 3 – Carbamazepine CYP3A Induction

Effects of itraconazole and carbamazepine on the pharmacokinetics of nirmatrelvir / ritonavir in healthy subjects

- Nirmatrelvir / ritonavir received emergency use authorization by the FDA for COVID-19, full approval May 2023

- Nirmatrelvir and ritonavir are both CYP3A substrates; ritonavir acts as PK booster

- CBZ Study: Open-label, fixed sequence, 2 periods
  - Period 1 – Nirmatrelvir / ritonavir 300/100 mg alone;
  - Period 2 – CBZ titration 100 mg BID (Day 1-3), 200 mg BID (Day 4-7), 300 mg BID (Day 8-15) with co-admin nirmatrelvir / ritonavir 300/100 mg (Day 14)
  - Exclusion of subjects shown to carry or be positive for HLA-B*1502 and HLA-A*3101

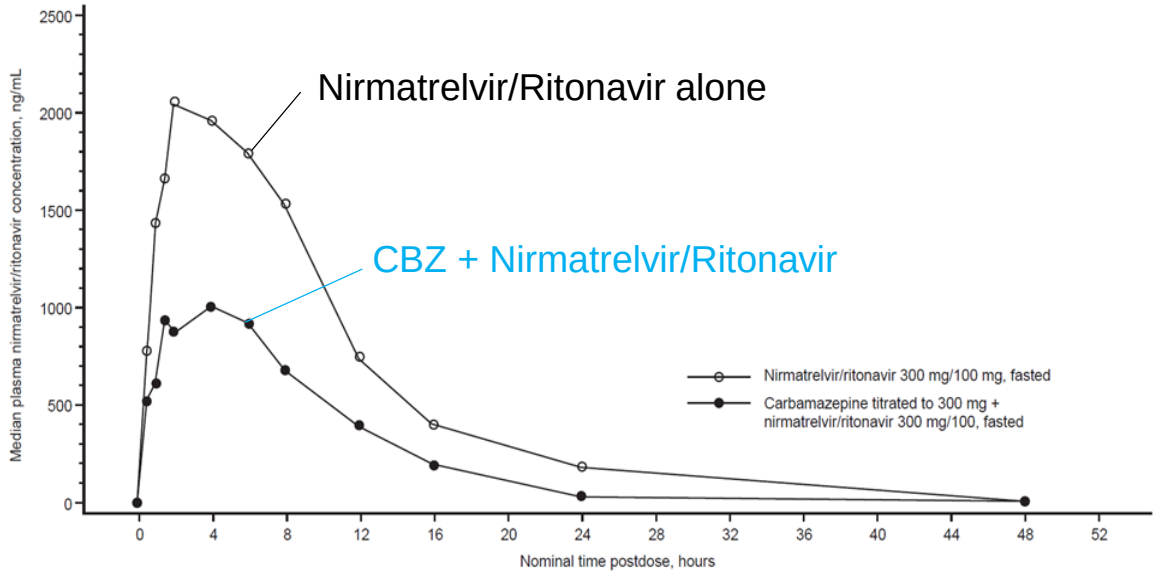
- ITZ Study: Open-label, fixed sequence, 2 periods
  - Period 1 – Nirmatrelvir / ritonavir 300/100 mg BID (Day 1-3) alone;
  - Period 2 – ITZ 200 mg (Day 1-8) with co-admin nirmatrelvir / ritonavir 300/100 mg BID (Day 4-6)

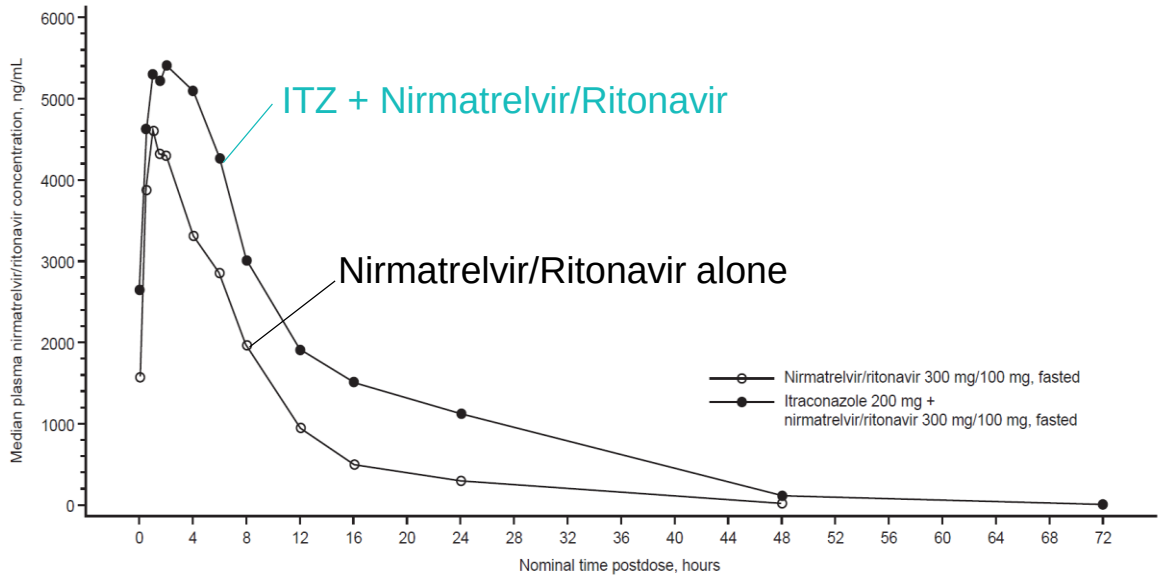
Cox et al. BJCP 2023. ClinicalTrials.gov Identifier: NCT04962230; NCT04962022

HLA, human leukocyte antigen

Case Study 3 – Moderate Induction and Inhibition Effect on Nirmatrelvir

Nirmatrelvir Concentration-Time Profiles



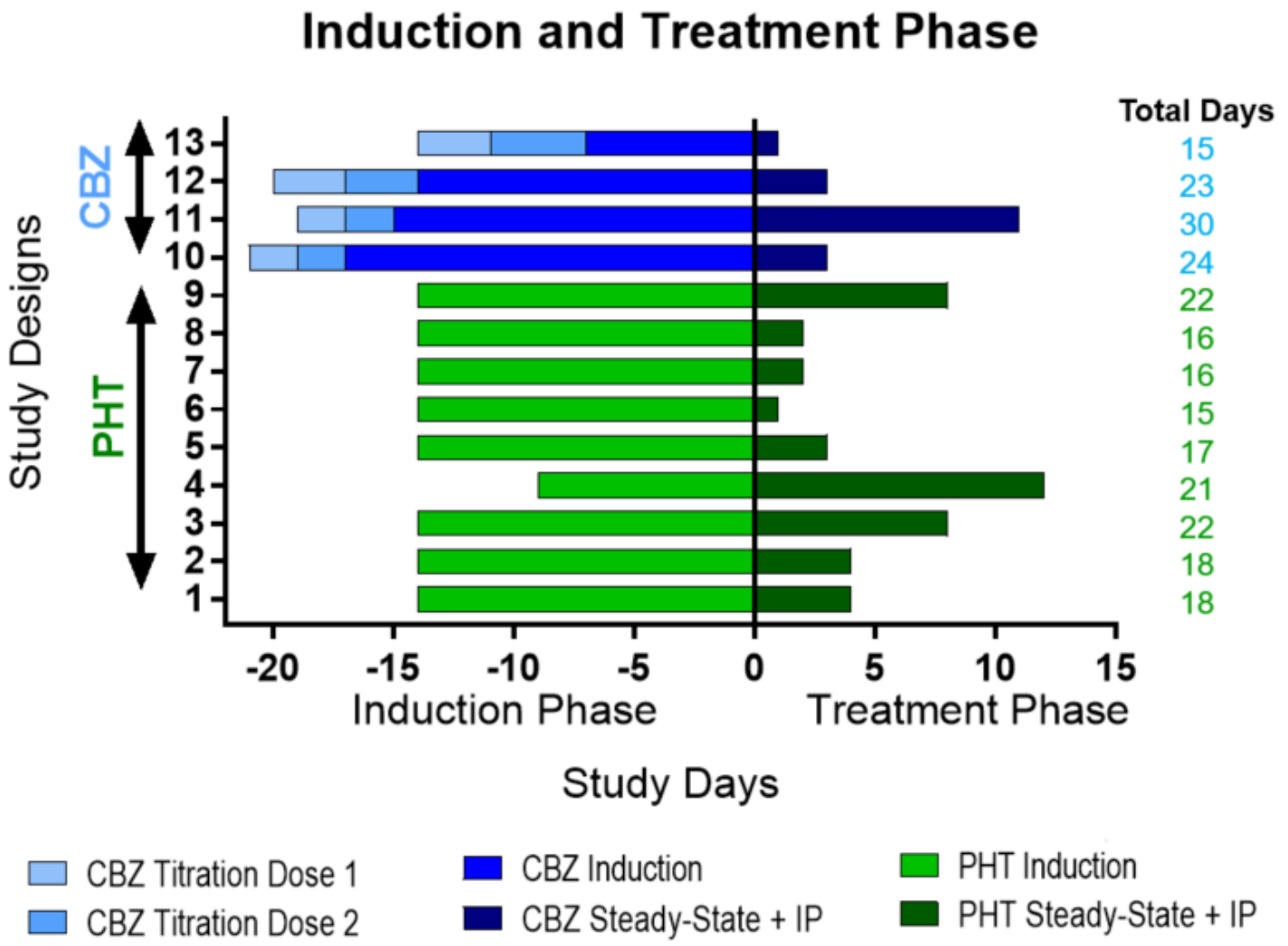


CBZ DDI Study Safety Results:

- No deaths, serious adverse events (SAEs) nor severe AEs
- CBZ generally well tolerated
- One participant discontinued from study due to moderate SIADH (Syndrome of Inappropriate secretion of Anti-Diuretic Hormone), related to CBZ in Period 2.

Cox et al. BJCP 2023

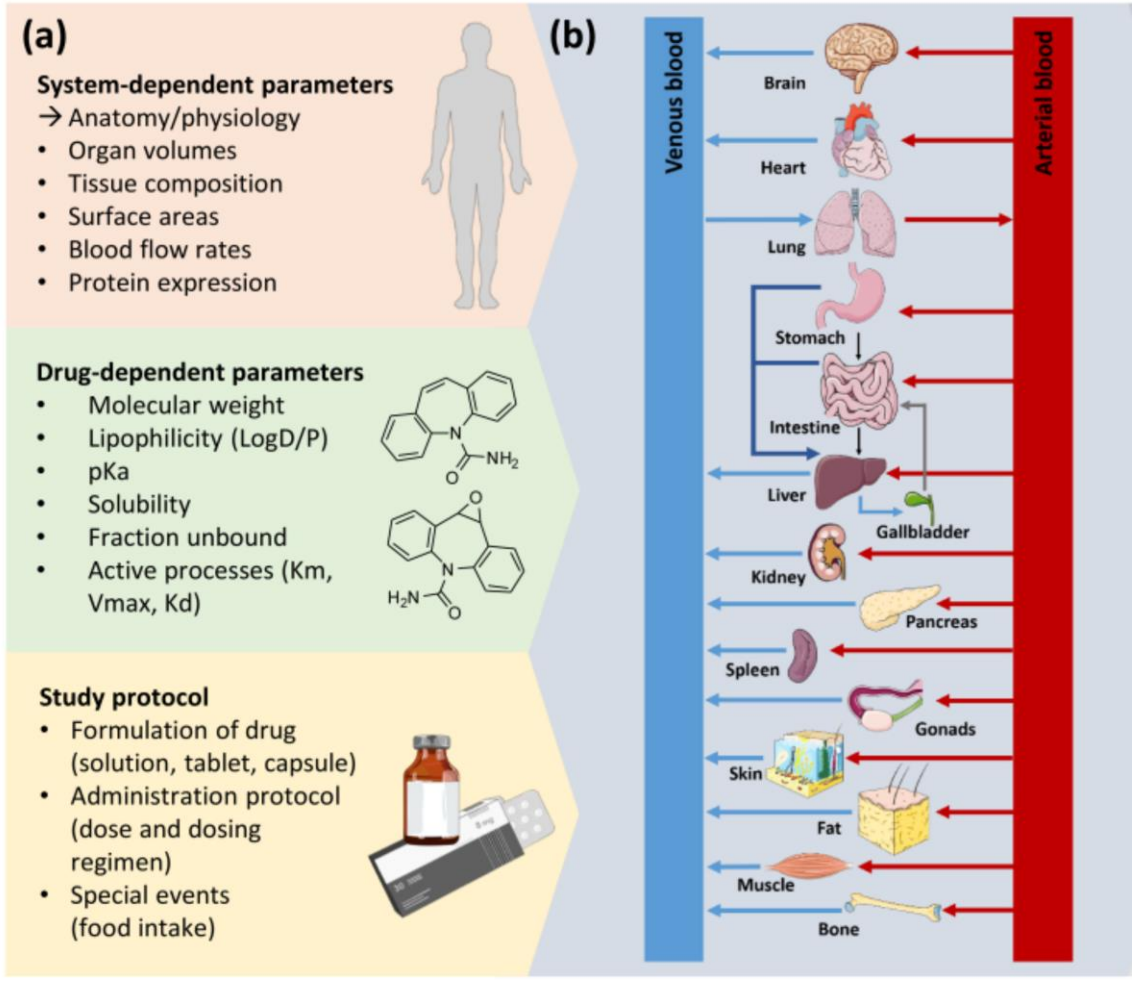
Period 2 Duration by Induction and Treatment Days



PBPK DDI Modeling

Physiologically Based Pharmacokinetic (PBPK) Modeling

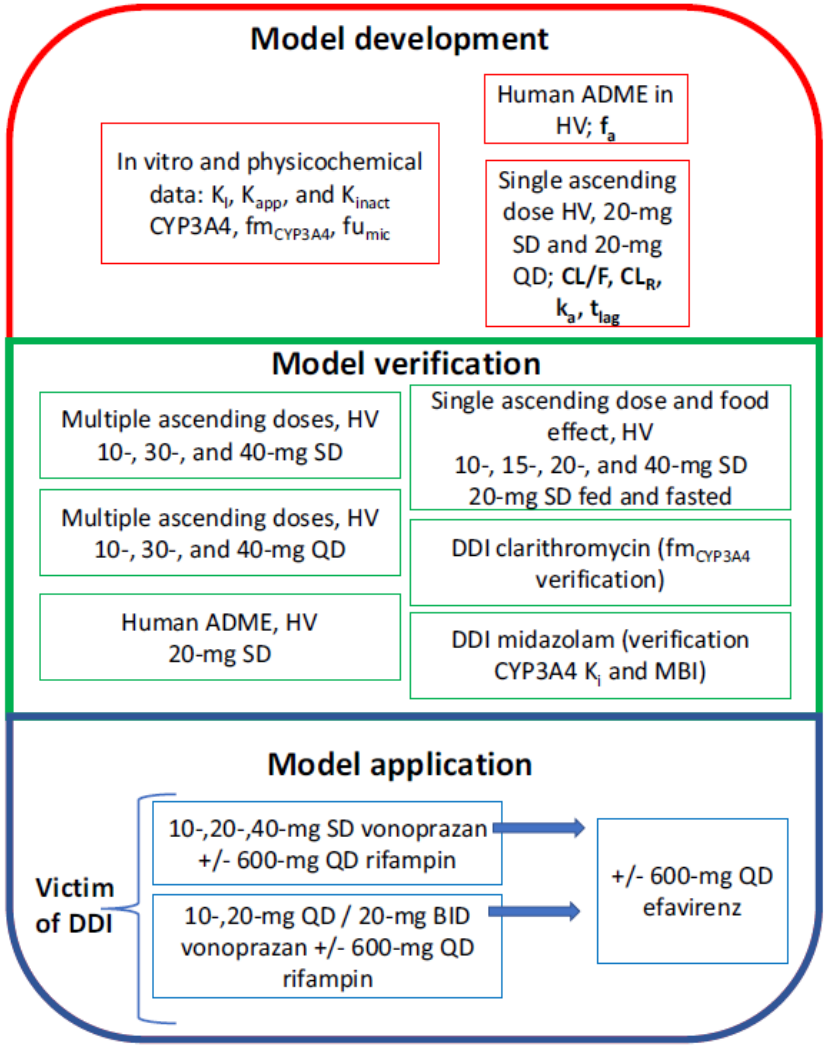
- Integration of physiological, system, chemical, and drug-dependent preclinical and clinical information
- Multi-compartment representing organs and blood flow
- Aim to simulate untested clinical scenarios
  - First in human dose exposure
  - Absorption
  - Food effect
  - **Drug-drug interaction**
  - Formulation
  - Special populations



Fuhr et al. Pharmaceutics 2021.

PBPK Model-Informed Labeling - Vonoprazan

- Potassium-competitive acid blocker
  - GERD, erosive esophagitis
- Dual and Triple Pak
  - Combined with amoxicillin and clarithromycin for the treatment of ***Helicobacter pylori*** infection in adults
- In vitro
  - CYP3A4 is primary metabolizing enzyme, minor CYP2D6 and CYP2C19 contribution
  - Inhibits CYP3A
- Plans for a clinical rifampin DDI study were halted due to nitrosamine issues
- Applied PBPK to simulate rifampin and efavirenz CYP3A induction, and inform drug label



Mulford et al. CPT: Pharmacometrics & Systems Pharmacology 2023.

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/215152Orig1s000,215153Orig1s000IntegratedR.pdf

Vonoprazan PBPK DDI Modeling

Table 113. Predicted and Observed Effects of CYP3A Perpetrators on Vonoprazan PK Following Co-administration of CYP3A Perpetrators With Single or Multiple Doses of Vonoprazan in Healthy Subjects

CYP3A inhibitors	Vonoprazan Dosing	$C_{max,inh}$ (ng/mL)	$AUC_{0\text{-}inf,inh}$ (ng/mL.h)	C_{max} Ratio	$AUC_{0\text{-}inf}$ Ratio	
Clarithromycin 500 mg BID 7 d	40 mg SD D6	63.7	648	1.35	1.58	Study TAK-438-110
		72.3	690	1.51	1.78	simulated
		1.14	1.06	1.12	1.13	Sim/obs
Clarithromycin 400 mg BID 7 d	20 mg BID 7d	70.2	538.8*	1.87	1.85*	Study TAK-438/CPH-401
		57.4	403.3*	1.28	1.36*	simulated†
		0.82	0.75	0.67	0.74	Sim/obs
Rifampin 600 mg QD 18d	20 mg SD D16	7.32	38.6	0.28	0.20	predicted
Rifampin 600 mg QD 16d	20 mg BID 16d	11.2	52.6	0.28	0.22	predicted
Efavirenz 600 mg QD 18d	20 mg SD D16	14.9	92.2	0.56	0.46	predicted
Efavirenz 600 mg QD 16d	20 mg BID 16d	21.6	116	0.54	0.46	predicted

Predicted 80% reduction

Predicted 50% reduction

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/215152Orig1s000,215153Orig1s000IntegratedR.pdf

Vonoprazan Label

Effect of CYP3A Inducers on Vonoprazan:

Vonoprazan ***exposures are predicted to be 80% lower*** when co-administered ***with a strong*** CYP3A4 inducer such as rifampicin and ***50% lower*** when co-administered with a ***moderate*** CYP3A4 inducer such as efavirenz.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215152s000,215153s000lbl.pdf

But….

Reviewer comments: The analyses may ***underestimate*** the induction effects of rifampin and efavirenz on vonoprazan PK. ***Confidence*** in induction prediction ***is low*** but is not a major concern in this case because the Applicant recommends ***avoiding co-administration*** of vonoprazan with strong or moderate CYP3A inducers in the product labelling

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/215152Orig1s000,215153Orig1s000IntegratedR.pdf

Nitrosamine Concerns

May 2022

Vonoprazan approved

But…

Aug 2022

Detected trace amounts of nitrosamine impurities, n-nitroso-vonoprazan (NVP)[1]

Jan 2023

Market launch delayed as company is working to reduce NVP below acceptable intake level of 96 ng/d[1]

Apr 2023

Root cause analysis and minor reformulation completed[2]

1. https://www.globenewswire.com/news-release/2023/01/03/2582483/0/en/Phathom-Pharmaceuticals-Provides-Update-on-New-Drug-Application-Review-of-Vonoprazan-for-Erosive-Esophagitis.html
2. https://investors.phathompharma.com/node/8631/pdf

Drugs Applying PBPK CYP3A Inducer Models Reviewed by the FDA (2018-2019)

Drug (NDA)	TA	Inducer Modeled	FDA Assessment[1]	Label[2]: CYP3A Inducers Co-admin.
Siponimod (209884)	Neurology	RIF and EFZ	Adequate	Strg not recommended
Prucalopride (210166)	Gastroenterology	RIF	Inadequate (model did not provide verification of RIF on P-gp & BCRP)	None
Avatrombopag (210238)	Hematology	RIF	Adequate (relevant studies supporting label)	None
Cannabidiol (210365)	Neurology	Redacted	Inadequate (metabolites not in model)	Consider dose ↑ with Strg
Encorafenib (210496)	Oncology	RIF	Inadequate (model lacked key clinical data to verify assumptions)	Avoid with Mod. & Strg
Doravirine (210806)	Anitviral and anti-infective	RIF, EFZ, RIB	Adequate (relevant studies supporting label)	RIF, PHT, CBZ contra-indicated. ↑ dose with RIB
Apalutamide (210951)	Oncology	RIF	Adequate	None
Duvelisib (211155)	Hematology	RIF	Adequate	Avoid with Strg
Ivosidenib (211192)	Hepatology	RIF and EFZ	Adequate	Avoid with Strg
Upadacitinib (211675)	Anesthesia, Analgesia, Pulm., Allergy, Rheuma.	RIF	Adequate (relevant studies supporting label)	Strg not recommended
Erdafitinib (212018)	Oncology	RIF	Adequate	Avoid with Strg. ↑ dose with Mod.
Fedratinib (212327)	Hematology	RIF and EFZ	Inadequate (uncertainties in predicting the net effect coming from CYP3A and CYP2C19)	Avoid with Mod. & Strg
Alpelisib (212526)	Oncology	RIF	Inadequate (uncertainties in predicting the net effect)	Avoid with Strg.
Voxelotor (213137)	Hematology	RIF and EFZ	Adequate	Avoid with Mod. & Strg
Zanubrutinib (213217)	Hematology	EFZ	Adequate (RIF DDI study conducted in HV)	Avoid with Mod. & Strg
Lefamulin (211672; 211673)	Antiviral and anti-infective	RIF and EFZ	Inadequate (uncertainty in model structure)	Avoid with Mod. & Strg
Entrectinib (212725; 212726)	Oncology	RIF and EFZ	Adequate	Avoid with Mod. & Strg

1. Adapted from: Zhang et al. JCP 2020. 2. Per drug label. **CBZ**, carbamazepine; **DDI**, drug-drug interaction; **EFZ**, efavirenz; **HV**, healthy volunteers; **Mod**, moderate inducer; **PHT**, phenytoin; **RIB**, rifabutin; **RIF**, rifampin; **Strg**; strong inducer

Summary

- Nitrosamine impurities continues to remain an issue for drugs in development
  - DDI studies – effect substrates, inhibitors and inducers
  - New drugs coming onto market need to preform risk assessment
- Alternative CYP3A inducers needed for DDI studies
  - “Clean” rifampin batches yet to be released
- Preferred alternatives include **PHT** & **CBZ**, while **EFZ** and LUM could also be considered
  - **PHT** and **CBZ** demonstrate similar reduction in substrate exposure
- **PHT** is a strong CYP3A inducer with good safety profile
  - Holds similar dynamic range on CYP3A as ITZ
- Dose titration and special mitigations steps required for **CBZ**
- PBPK may be an alternative approach for well-verified, robust models

Thank You!

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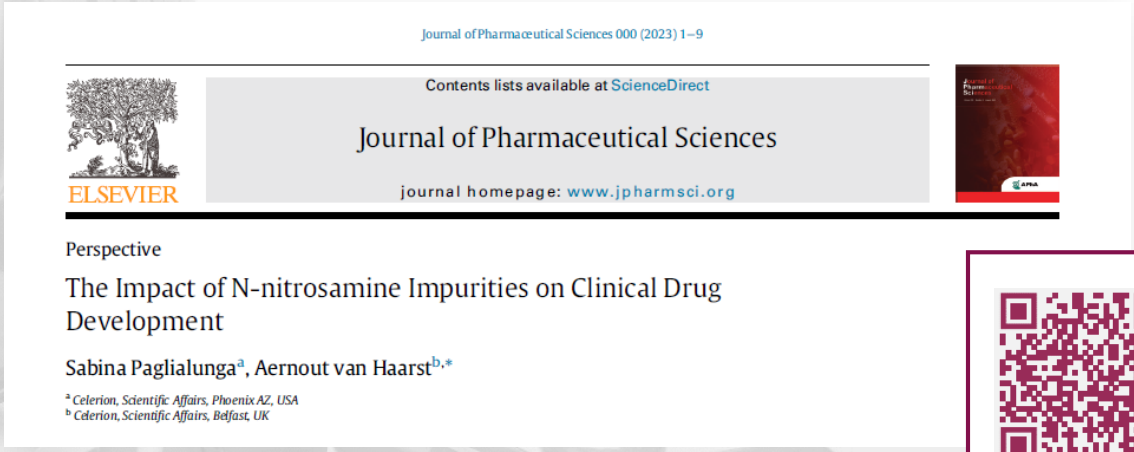
Check out our recent articles on nitrosamine impurities:



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Perspective

The Impact of N-nitrosamine Impurities on Clinical Drug Development

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CLINICAL PHARMACOLOGY & THERAPEUTICS

MINI-REVIEW

Rifampin Drug–Drug–Interaction Studies: Reflections on the Nitrosamine Impurities Issue

Aernout van Haarst[1,*], Stephen Smith[2], Clare Garvin[2], Natacha Benrimoh[3] and Sabina Paglialunga[4]