

# Phenytoin: A Safe and Potent Alternative to Rifampin as CYP3A Inducer in Drug-Drug-Interaction Studies

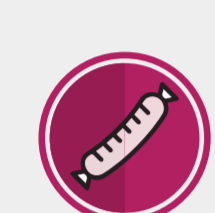
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## BACKGROUND

- Rifampin, an antibacterial drug used to treat tuberculosis, is a strong CYP3A inducer and often administrated as a perpetrator in drug-drug interaction (DDI) studies.
- Due to recent N-nitrosamine impurity findings in marketed rifampin formulations, its application in healthy volunteer DDI studies was halted in 2020.
- While there are a number of putative rifampin alternatives (Table 1), phenytoin remains the most viable option for healthy volunteer DDI studies.
- We reviewed published studies to provide a comprehensive characterization of phenytoin-induced changes in drug exposure as well as its safety profile.

### Box 1. Rifampin Impurity Issue



N-nitrosamines are common and present in low levels in food, beverages, cosmetics, water and tobacco products.



However, above acceptable intake limits (AIL), they are regarded as a "cohort of concern" in ICH M7 due to their high mutagenic and carcinogenic potential.



1-methyl-4-nitrosopiperazine (MNP) levels in rifampin capsules were found above the AIL of 0.16 parts per million (ppm).



To avoid drug shortages and allow patients to continue with lifesaving rifampin treatment, the FDA indicated that they would not object to MNP levels up to 5 ppm. However, regulatory agencies will not accept the use of rifampin for healthy volunteer DDI studies.

Table 1: Alternative CYP3A4 Perpetrators

Perpetrator	Drug Type and Indication	Effects on Other CYPs	Comments	Suitable Rifampin Replacement
Apalutamide	Nonsteroidal antiandrogen non-metastatic, castration-resistant prostate cancer	Strong inducer of CYP2C19; weak inducer of CYP2C9*	Increased risk of seizure; increased incidence of fall and fractures*	✗
Carbamazepine	Sodium channel blocker, anticonvulsant	Strong inducer of CYP2B6; weak inducer of CYP2C9	Dose titration recommended to mitigate side effects. Black box warning for serious (potentially fatal) dermatologic reactions	✗
Enzalutamide	Nonsteroidal antiandrogen, prostate cancer	Moderate inducer of CYP2C9 and CYP2C19	Increased risk of seizure; increased incidence of fall and fractures**	✗
Mitotane	Adrenal cytotoxic agent, Cushing's syndrome and adrenal cortical carcinoma		Common adverse reactions (>15%) include: anorexia, nausea, vomiting and diarrhea; depression, dizziness or vertigo; and rash ***	✗
Phenytoin	Sodium channel blocker, anticonvulsant	Strong inducer of CYP2C19; moderate inducer of CYP1A2, CYP2B6, CYP2C8, CYP2C9	Preferred perpetrator	✓
Rifabutin	Antimicrobial, tuberculosis and chronic staphylococcal infections	Weak inducer of CYP3A4	MHRA recommendation; not an option listed by FDA	✗
St. John's wort	Herbal supplement derived from Hypericum perforatum plant		Effect varies widely and is preparation-dependent	✗

Adapted from FDA <https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers> Table 3-3. \*per Erelada (Apalutamide) label; \*\*per Xtandi (Enzalutamide) label; \*\*\*per Lysodren (Mitotane)

## METHODS

- A literature review of clinical trials revealed 16 studies evaluated the effect of phenytoin as a perpetrator on drug substrates. Four studies included patients, the remainder enrolled healthy volunteers.
- For each substrate, Area-Under the Curve (AUC) fold change and 95% confidence intervals (CI) were calculated if not reported.
- Phenytoin results were compared to published rifampin DDI findings, if available.
- Available safety findings for phenytoin were summarized.

Table 2. Summary of Phenytoin DDI Studies

Substrate Drugs	Predominant Metabolizing CYP*	Study Population	Substrate Dose	Phenytoin Dose
Celecoxib [1]	CYP2C9	22 Glioblastoma patients	400 mg BID	Chronic anti-seizure medication (including Phenytoin)
Clinafloxacin [2]	Hepatic metabolism	16 HV	200 or 400 mg BID; 5 & 21 days	100 mg TID; 21 days
Digoxin [3]	P-gp	6 Male HV	1 mg IV & 0.4 mg b-acetyldigoxin PO for 7 days	200 mg BID; 7 days
Lopinavir (LPV) / Ritonavir (RTV) [4]	CYP3A	12 HV	LPV/RTV 400/100 mg BID; 11 days	300 mg QD; 11 & 23 days
Tirilazad mesylate [5]	CYP3A [5]	12 Male HV	1.5 mg/kg IV, every 6h for 5 days (21 doses)	200 mg TID; 16 doses
Bromfenac [6]	CYP2C9	12 Male HV	50 mg TID; 4 days	300 mg QD; 7 & 14 days
Mirtazapine [7]	CYP3A	19 Male HV	15-30 mg QD; 15 days	200 mg QD; 10 days
Gefitinib [8]	CYP3A4	18 Male HV	250 mg SD	2.5 mg/kg BID; 7 days
Posaconazole [9]	P-gp	36 HV	200 mg QD; 10 days	200 mg QD; 10 days
Atorvastatin [10]	CYP3A4 and transporters (OATP1B1/1B3, P-gp, or BCRP)	44 HV	40 mg QD; 7 days & 3 weeks	4 mg/kg QD; 3 weeks
Losartan [11]	CYP2C9 and CYP3A4	16 HV	50 mg QD; 9 days	4 mg/kg (max 400 mg/d); 9 days
Ivabradine [12]	CYP3A4	18 Male HV	10 mg SD	150 mg BID; 5 days
Voriconazole [13]	CYP2C19	21 Male HV	200 mg BID; 7 & 21 days	300 mg QD; 7 days
Quetiapine [14]	CYP3A4	17 Schizophrenic patients	Dose escalation to 250 mg TID; 10 days	100 mg TID; 10 days
Nisoldipine [15]	CYP3A4	12 Epilepsy patients vs 12 HV	40 and 20 mg SD	Chronic administration
Midazolam [16]	CYP3A4	6 Epilepsy patients vs 7 HV	15 mg SD	Chronic anti-seizure medication (including Phenytoin)

\*Per drug label. BID = twice daily; HV = healthy volunteer; IV = intravenous; PO = by mouth; QD = once daily; SD = single dose; TID = three time per day

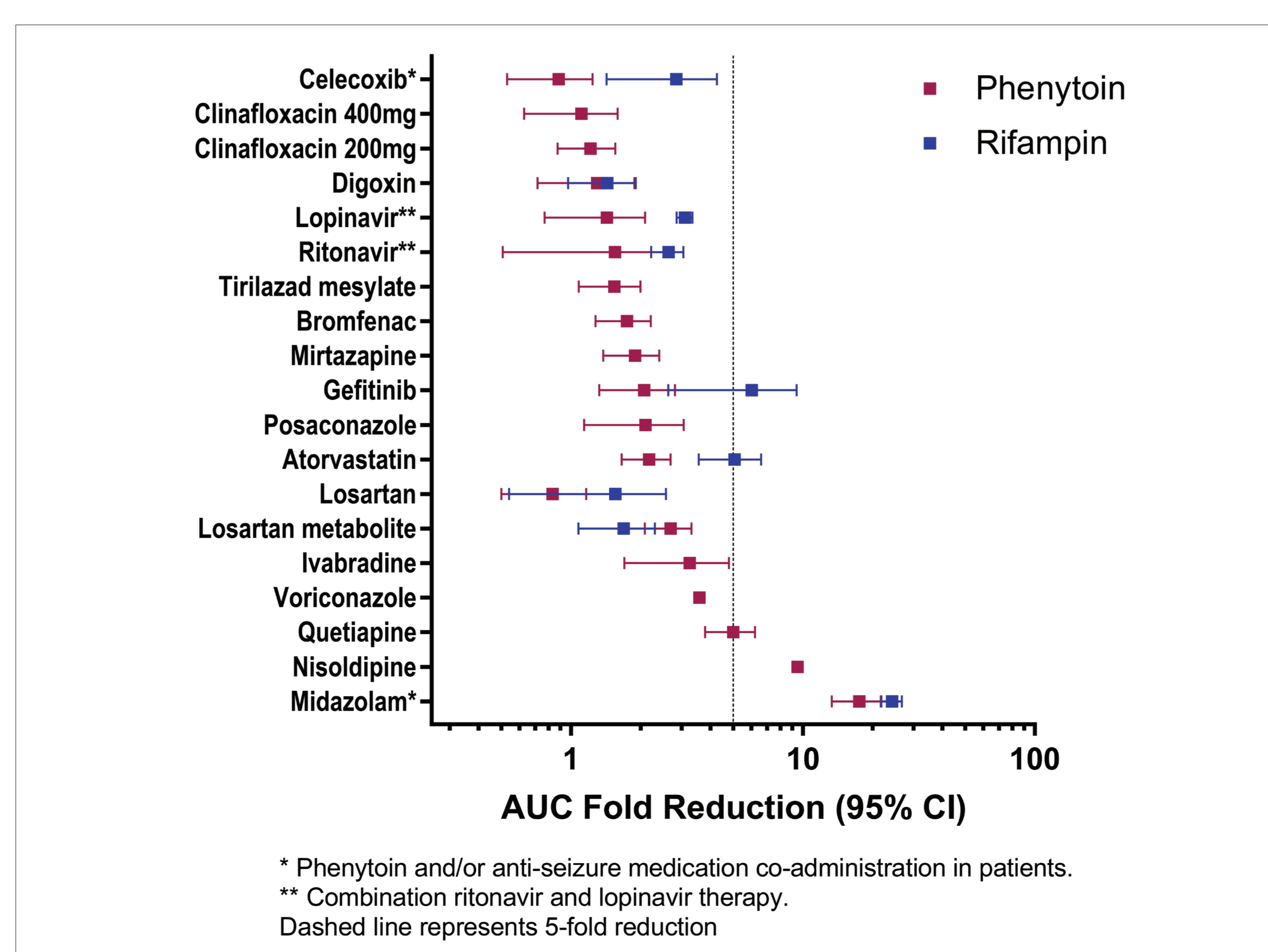
Table 3. Summary of Rifampin DDI Studies

Substrate Drug*	Study Population	Substrate Dose	Rifampin Dose
Celecoxib [17]	12 Male HV	200 mg QD; SD & 5 days	600 mg QD; 5 days
Digoxin [18]	8 Male HV	1 mg SD PO or IV	600 mg QD; 15 days
Losartan [19]	10 HV	50 mg QD; 7 days	300 mg BID; 7 days
Lopinavir (LPV) –Ritonavir (RTV) [20]	19 HIV patients	LPV/RTV 400 mg/100 mg BID; 1 & 8 days	600 mg QD; 8 days
Gefitinib [21]	18 Male HV	500 mg QD; 10 days	600 mg QD; 16 days
Atorvastatin [22]	10 HV	40 mg SD	600 mg QD; 5 days
Midazolam [23]	10 HV	15 mg SD	600 mg QD; 5 days

\*List of studies in which a phenytoin DDI was also conducted. BID = twice daily; HV = healthy volunteer; HIV = human immunodeficiency virus; IV = intravenous; PO = by mouth; QD = once daily; SD = single dose

## RESULTS

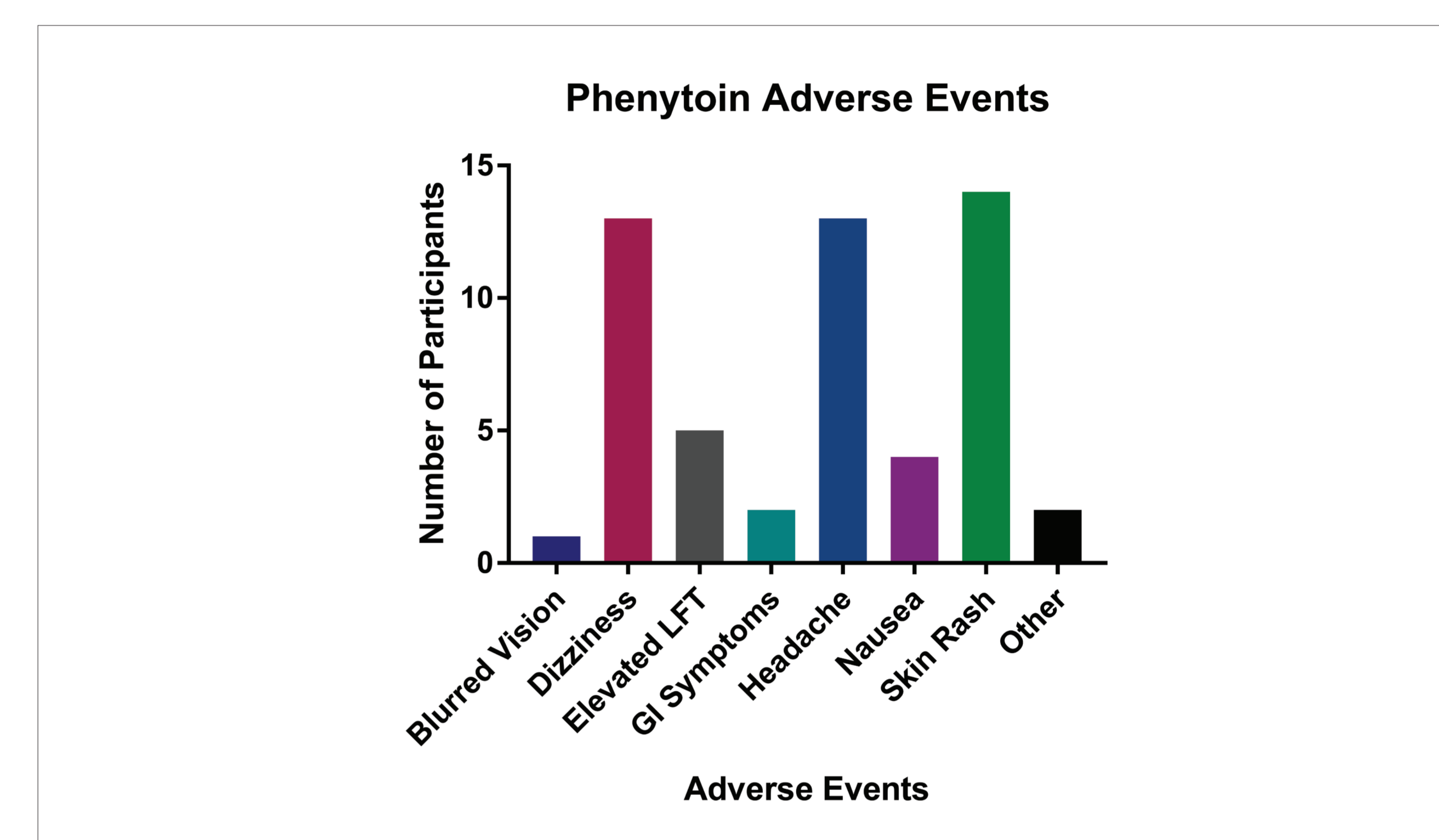
Figure 1. Phenytoin and Rifampin Induced AUC-Fold Change



\* Phenytoin and/or anti-seizure medication co-administration in patients.  
\*\* Combination ritonavir and lopinavir therapy.  
Dashed line represents 5-fold reduction

- Substrates cover a wide range of CYP3A4 sensitivity, with midazolam, nisoldipine, quetiapine being most sensitive.
- Digoxin and celecoxib represent P-gp and CYP2C9 induction, respectively.
- Overall, phenytoin resulted in an average (95% CI) AUC-fold reduction of 3.2 (1.3, 5.2).

Figure 2. Dizziness, Headache and Skin Rash Are the Most Common Phenytoin Related Adverse Events



- Phenytoin-related adverse events were mild to moderate, and transient in nature.
- The most common AEs included skin rash and dizziness, as reported in 7 and 5 studies, respectively.

## SIGNIFICANCE

- Rifampin will need to be replaced by alternative perpetrators for application in DDI studies until sufficient and uncontaminated batches become available.
- In the meantime, the use of phenytoin as an inducer of CYP3A4 has been shown to be effective.
- A recommended dose regimen of 100 mg TID (total daily dose 300 mg/day) for at least 14 days was found to be generally safe and well tolerated in healthy subjects.

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### Box 2.



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