A Drug-Drug Interaction Study to Investigate the Effect of Givosiran on the activity of 5 major drug metabolizing CYP450 enzymes in Subjects with Acute Intermittent Porphyria (AIP) who are Chronic High Excreters (CHE)

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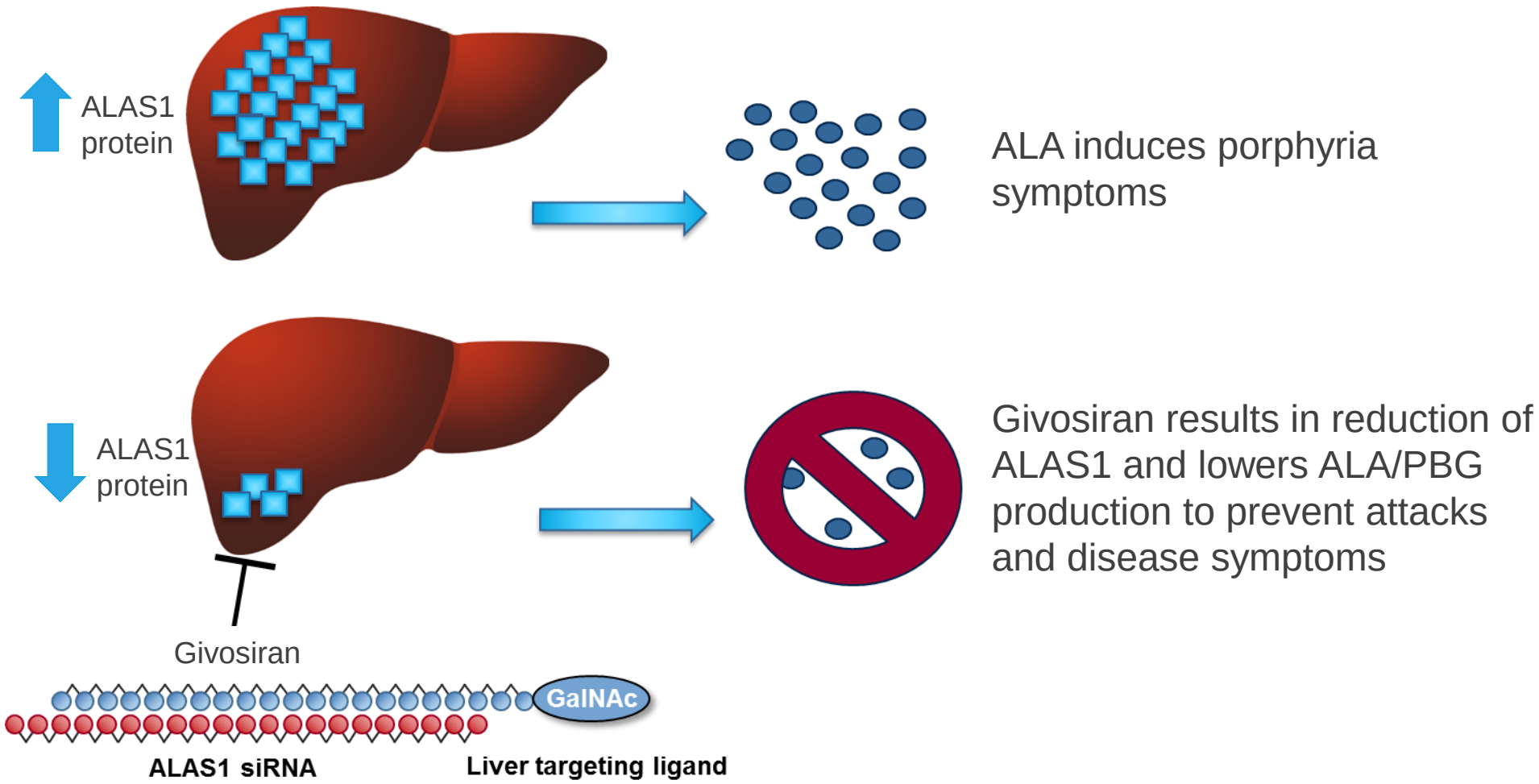
Givosiran: Investigational RNAi Therapeutic for AHP

Therapeutic Hypothesis

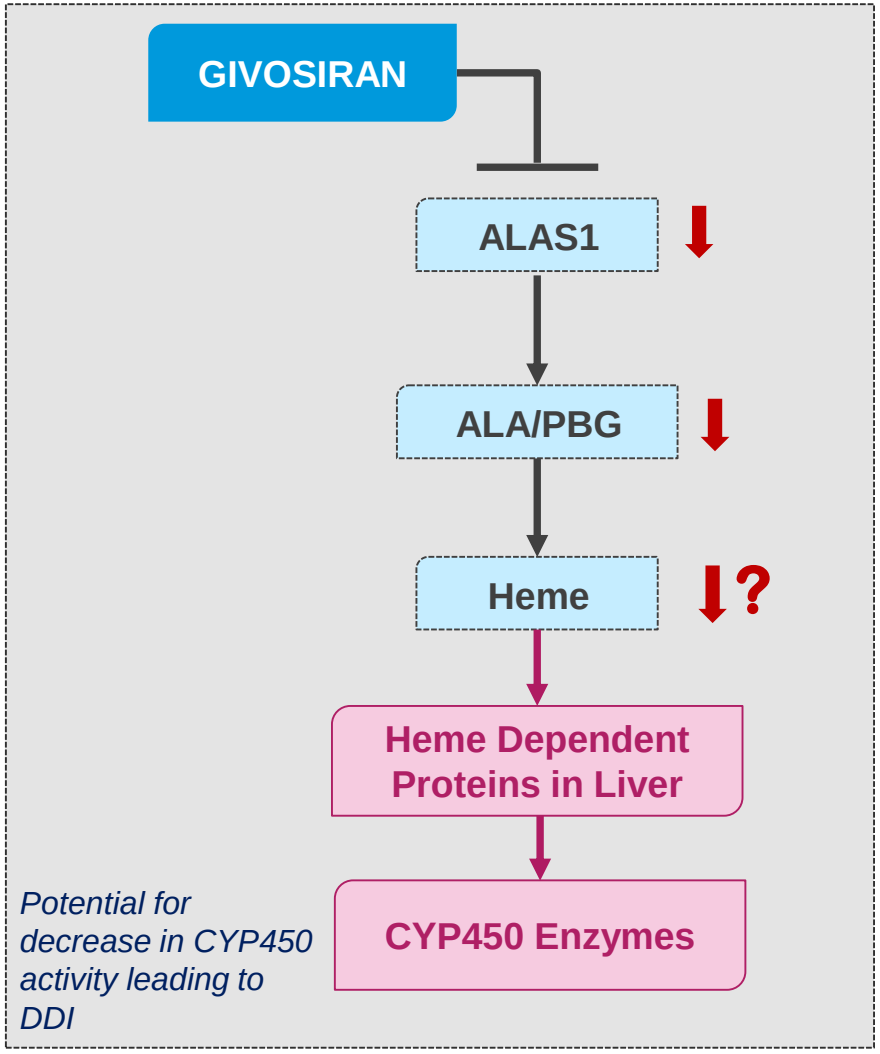
- Reduction of Liver ALAS1 Protein to Lower ALA and PBG



AHP, Acute hepatic porphyria; ALA, Aminolevulinic acid; ALAS1, ALA synthase 1; PBG, Porphobilinogen

Givosiran Has Potential to Impact Activity of Drug Metabolizing Enzymes

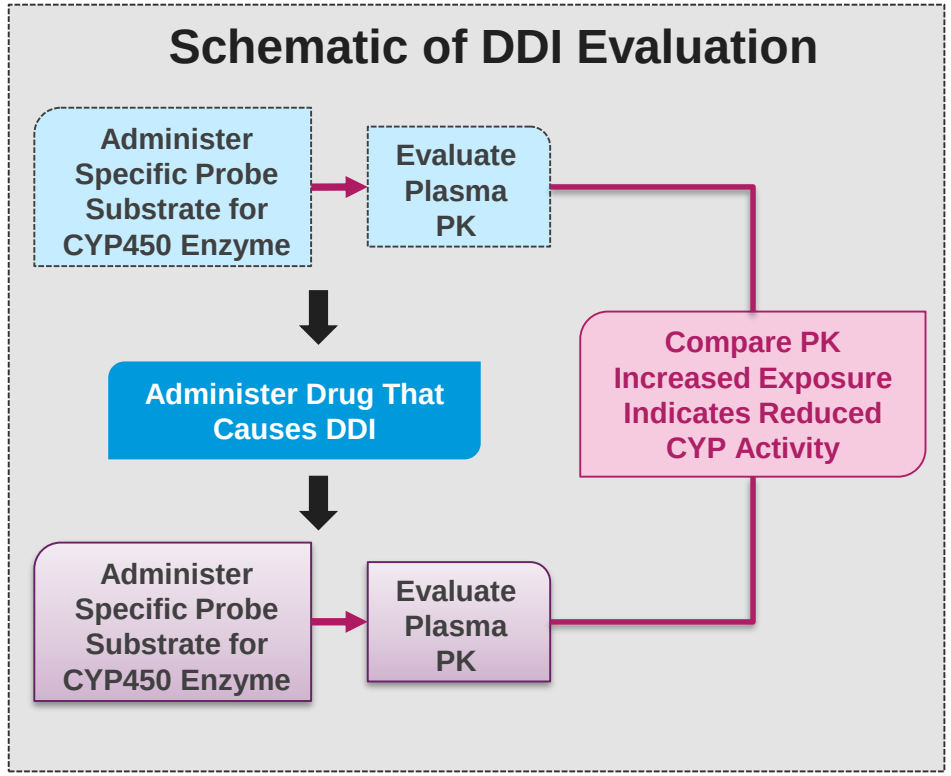
- Givosiran inhibition of ALAS1 mRNA, the first and rate limiting enzyme in heme biosynthesis pathway in liver, could potentially lower hepatic heme content
- Givosiran does not impact heme biosynthesis in bone marrow which is controlled by ALAS2; givosiran does not inhibit ALAS2
- Lowered hepatic heme levels could reduce activity of heme-dependent proteins in liver such as drug metabolizing cytochrome P450 (CYP450) enzymes
  - Majority of hepatic heme is incorporated in CYP450 enzymes
- Results from in vivo monkey studies were inconclusive but suggested potential impact on CYP3A4 activity



DDI, drug-drug interactions
Correia MA. Drug Metab Rev. 2011 Feb;43(1):1-26.

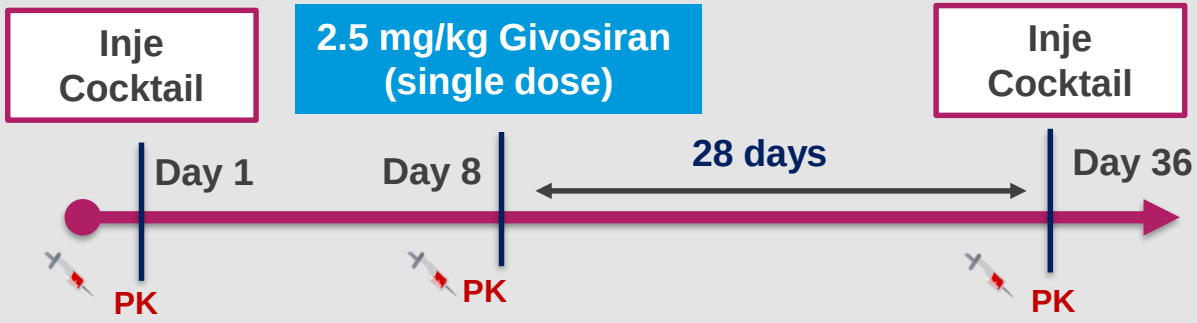
Pharmacokinetic Drug-Drug Interactions

- CYP450s are the major family of drug metabolizing enzymes
  - 5 enzymes (CYP 3A4, 2C19, 1A2, 2C9, 2D6) metabolize ~80% of clinically used drugs[1]
  - Age, sex, ethnicity, genetic polymorphisms, and disease influences activity
- Pharmacokinetic (PK) drug-drug interaction (DDI) important for drugs metabolized by CYP450s
  - Increased CYP450 activity can decrease drug exposure → potential altered effectiveness
  - Reduced CYP450 activity can increase drug exposure → potential altered safety profile
- Polypharmacy common in AHP patients due to multiple comorbidities, such as chronic pain, depression and hypertension



[1]. Zanger UM. Pharmacol Ther. 2013 Apr;138(1):103-41.

Design of Givosiran DDI Study



Inje Cocktail Components:

- 5 mg Midazolam (CYP3A4)
- 40 mg Omeprazole (CYP2C19)
- 200 mg Caffeine (CYP1A2)
- 50 mg Losartan (CYP2C9)
- 30 mg Dextromethorphan (CYP2D6)

- Inje cocktail used to simultaneously evaluate effect of givosiran on 5 major CYP450 enzymes[1]
- CHE subjects have relevant enzyme defect and elevated ALAS1/ALA/PBG enabling evaluation of givosiran pharmacodynamics and are on less medications than AHP patients with attacks
- Statistical analysis determined 10 subjects sufficient to detect a significant change in exposure of probe substrates
- Sequential (each patient their own control) study in 10 CHE subjects
- Dose of Inje cocktail on Day 1 (Baseline) and Day 36 (post-givosiran)
  - 2.5 mg/kg single dose of givosiran on Day 8
  - 28-day window post givosiran administration to enable maximal ALAS1/ALA reduction

Clinical Trials: NCT03505853

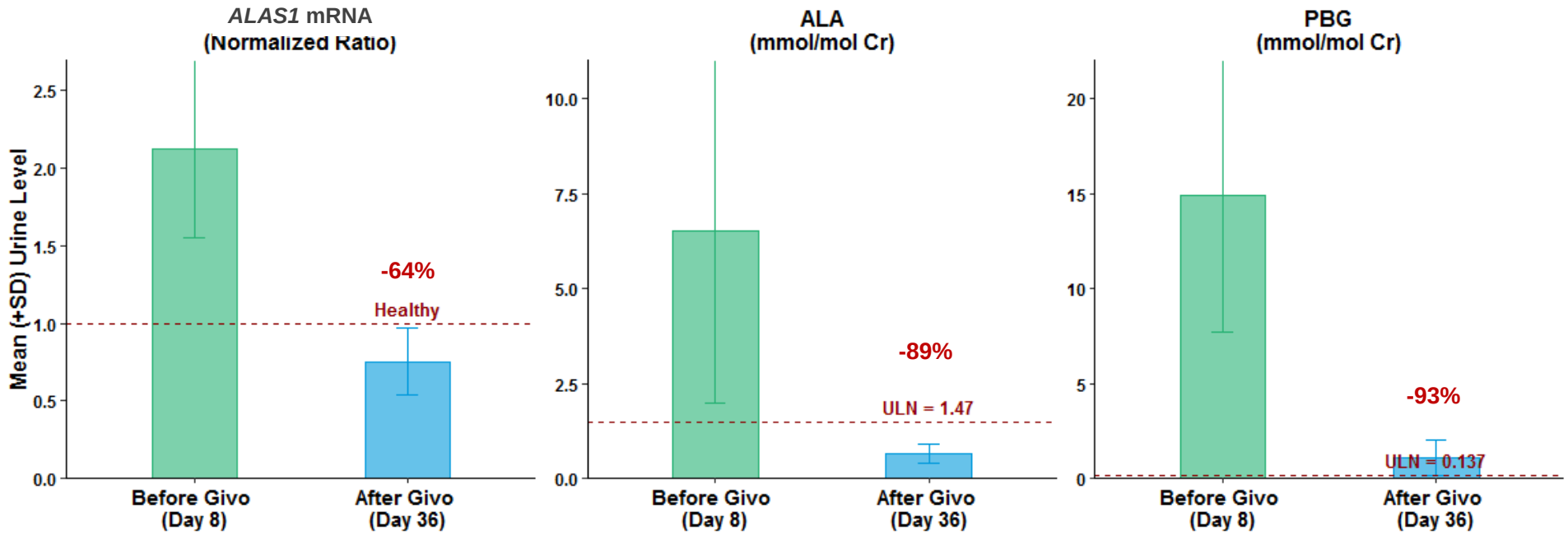
[1] Ryu JY. *Clin Pharmacol Ther*. 2007 Nov;82(5):531-40.

Subject Disposition and Demographics

Patients Enrolled	10
Patients Completed	9 (1 discontinued treatment due to non-safety reasons)
Age, median (range)	49 years (39-59)
Sex	7 Females, 3 Males
Race	Caucasian
Baseline ALAS1 Levels	2.13[1]
Baseline ALA Levels[2]	7.14 mmol/mol Cr
Baseline PBG Levels[2]	14.6 mmol/mol Cr
CYP2C9 Phenotype	Normal (n = 6), Intermediate Metabolizers (n = 4)
CYP2C19 Phenotype	Normal (n = 8), Intermediate Metabolizers (n = 2)
CYP2D6 Phenotype	Normal (n = 6), Intermediate Metabolizers (n = 4)

1 Ratio relative to healthy subjects
2 Upper Limit of Normal: ALA=1.5 mmol/mol Cr; PBG=0.14 mmol/mol Cr determined based on samples collected from 150 normal healthy subjects analyzed by LC-MS/MS. LC-MS-MS assay performed at a central laboratory (Covance, Utah).

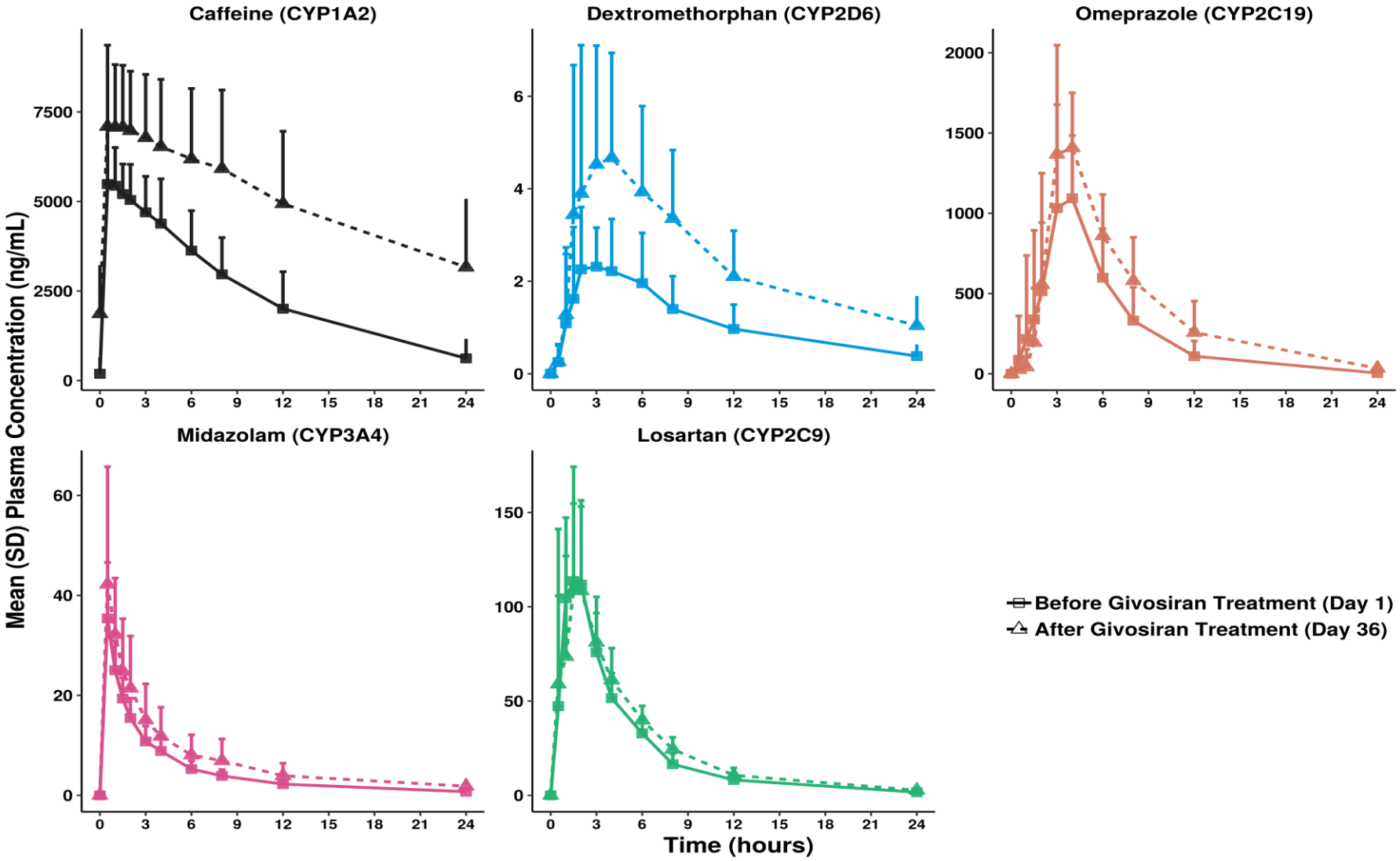
Maximum PD Effect of Givosiran was Achieved at time of DDI Evaluation



- Maximum PD effect of givosiran was achieved by Day 36, when DDI was evaluated
  - Urine *ALAS1* mRNA levels lowered by 64% compared to baseline, urine ALA levels lowered by 89% and PBG levels lowered by 93% compared to baseline
  - Residual *ALAS1* mRNA, ALA and PBG post-givosiran dosing similar to levels achieved in AHP patients with attacks

Ratio of 1 for *ALAS1* represent healthy levels since *ALAS1* levels in urine are normalized to healthy subject levels
Upper Limit of Normal (ULN) for ALA = 1.47 and PBG = 0.137 based on determination of levels in healthy subjects
Chan A. Mol Ther Nucleic Acids. 2015 Nov 3;4:e263.

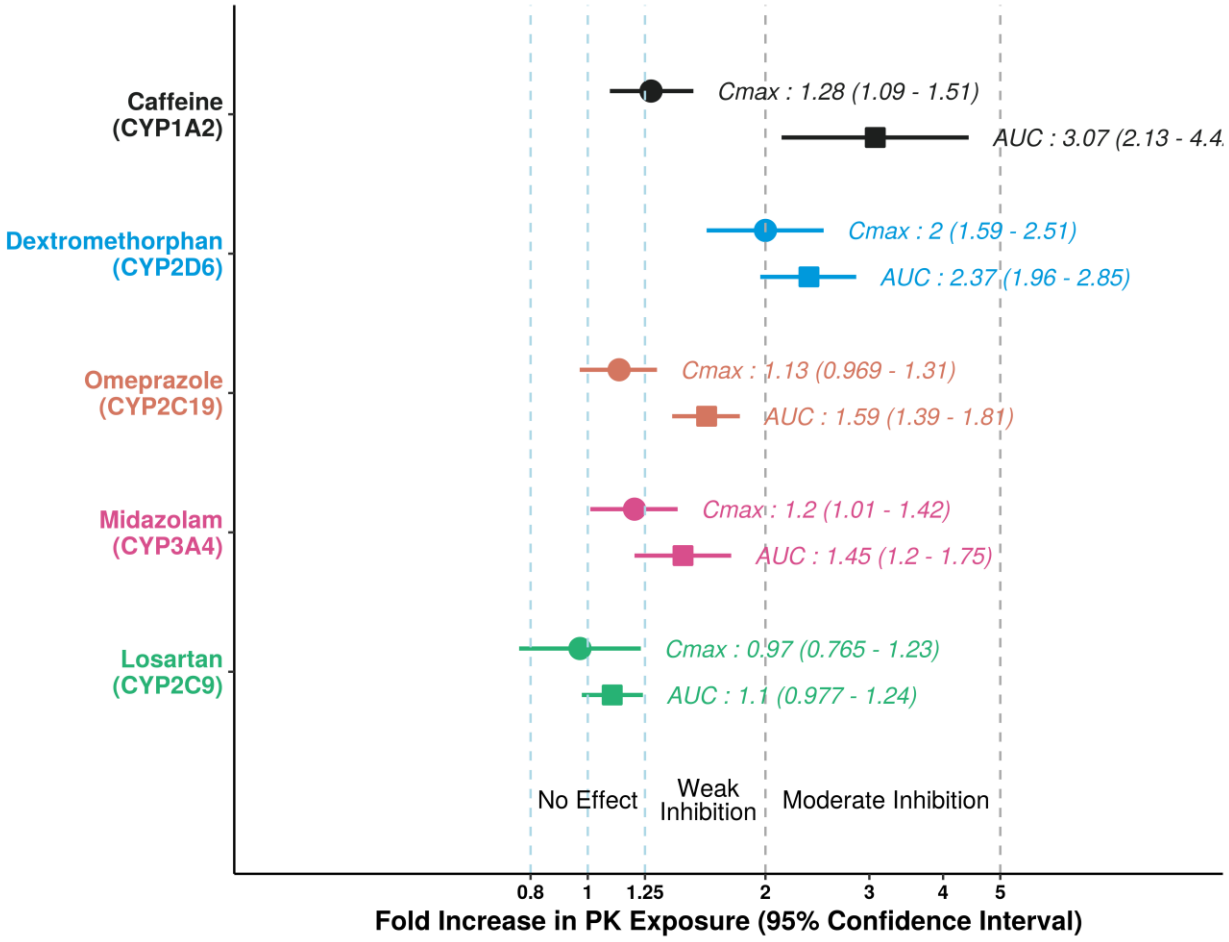
Impact of Givosiran Treatment on CYP450 Enzyme Activity



Solid lines are baseline and dotted lines are post-givosiran

Nakashima D. *J Clin Pharmacol*. 2007 Oct;47(10):1311-9; Ishii Y. *Clin Transl Sci*. 2018 Sep; 11(5): 477–486; Bosilkovska M. *Basic Clin Pharmacol Toxicol*. 2016 Sep;119(3):284-90.

Givosiran Treatment had Variable Impact on CYP450 Enzyme Activity



- Moderate inhibitory effect on CYP1A2 and 2D6
  - Caffeine AUC increased 3.1-fold and dextromethorphan AUC increased 2.4-fold after givosiran treatment
- Weak inhibitory effect on CYP3A4 and 2C19
  - Midazolam and omeprazole AUC increased 1.6-fold and 1.5-fold, respectively, after givosiran treatment
- No effect on CYP2C9
  - Losartan AUC was unchanged after givosiran treatment

FDA/EMEA guidance: moderate inhibitors increase the AUC ≥2 to <5-fold; weak inhibitors increase AUC ≥1.25 to <2-fold

Medications Commonly Used in Symptomatic AHP Patients

- Highest impact of DDI may be on drugs primarily metabolized by CYP2D6
  - CYP2D6 metabolized drugs typically titrated slowly given genetic polymorphisms common in population, leading to extensive variation in CYP2D6 activity (e.g. 50-fold variability in tricyclic antidepressant levels)
- Very few drugs metabolized by CYP1A2
- Minor impact on CYP3A4 and CYP2C19 is unlikely to be clinically significant/relevant

Common Comedications in AHP	
Pain Management: Opioid Analgesics, NSAIDs, Triptans	CYP2D6
Antidepressants (TCAs, SSRIs, SNRIs)	
Antipsychotics	
Antianxiety (Benzodiazepines)	CYP3A4
Antihypertensives (ARBs, ACE inhibitors, betablockers)	
Gastrointestinal Agents (PPIs, anti-emetics)	CYP2C19
Corticosteroids, Statins	
Gabapentin, Pregabalin, Anticonvulsants	

Few drugs used metabolized by CYP1A2 (e.g. theophylline)

Most commonly used comedications in ENVISION, a Phase 3 Study of Givosiran in Patients with AHP

Summary

- Givosiran treatment had a variable impact on CYP450 enzyme activity
  - Moderate reduction in activity of CYP1A2 and CYP2D6
  - Weak reduction in activity of CYP2C19 and CYP3A4
  - No effect of on activity of CYP2C9
- Patients on drugs with a narrow therapeutic index primarily metabolized by CYP2D6 or CYP1A2 may need to be monitored more frequently to determine if dose adjustment of a concomitant medication is required

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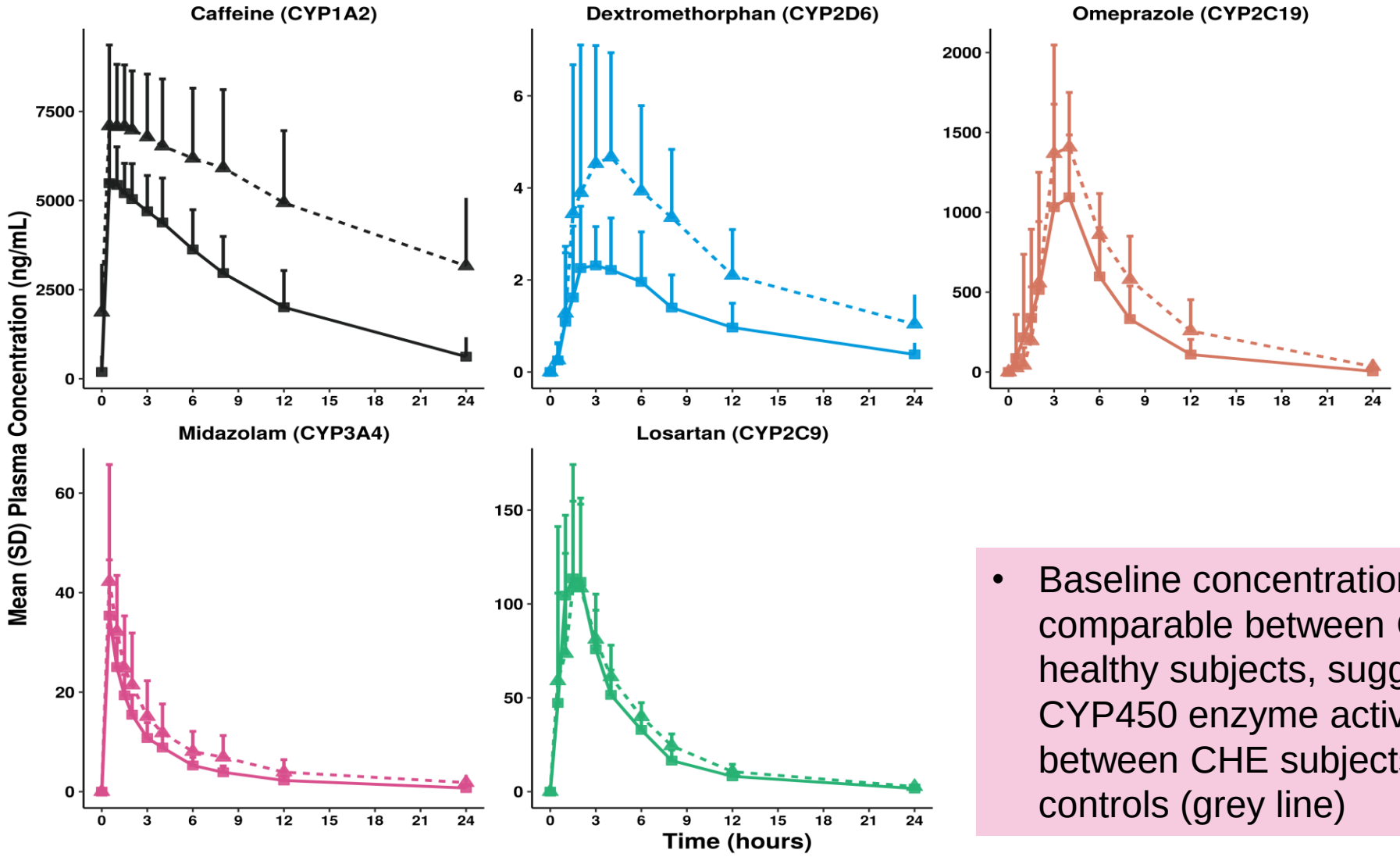

- Baseline concentration-time profiles comparable between CHE subjects and healthy subjects, suggesting that CYP450 enzyme activity is consistent between CHE subjects and healthy controls (grey line)

Solid lines are baseline and dotted lines are post-givosiran

Nakashima D. *J Clin Pharmacol*. 2007 Oct;47(10):1311-9; Ishii Y. *Clin Transl Sci*. 2018 Sep; 11(5): 477–486; Bosilkovska M. *Basic Clin Pharmacol Toxicol*. 2016 Sep;119(3):284-90.