Bristol-Myers Squibb HCV DAAs: Review of Interactions Involving Transporters

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Disclosures

- T Eley is a full time employee and stockholder of Bristol-Myers Squibb

Background: Asunaprevir (ASV, BMS-650032)

- Potent, selective inhibitor of the HCV NS3 protease
  - Clinical data in HCV genotypes (GTs) 1 and 4
  - Generally well tolerated in studies with > 2000 patients

- Currently under FDA review as part of a combination regimen for HCV with daclatasvir (DCV; NS5A inhibitor) and in Phase 3 as part of an all-oral regimen with DCV and BMS-791325 (non-nucleoside NS5B polymerase inhibitor)

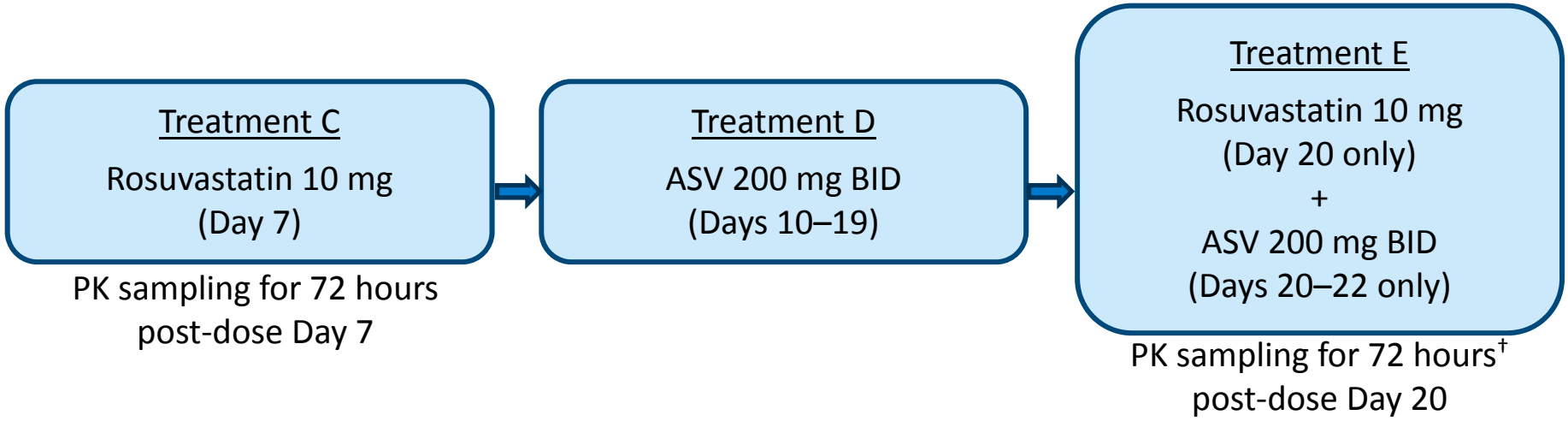
- Steady state plasma C_{max} for 100 mg BID Phase 3 softgel capsule was 572 ng/mL with CV of 75% in US Phase 3 study (Asians are ~1.5-2x higher)
  - Plasma protein binding of ~99.8%
  - High liver:plasma ratio in animals (40–1240x); NS3 PI class related

ASV *in vitro* Transporter Data

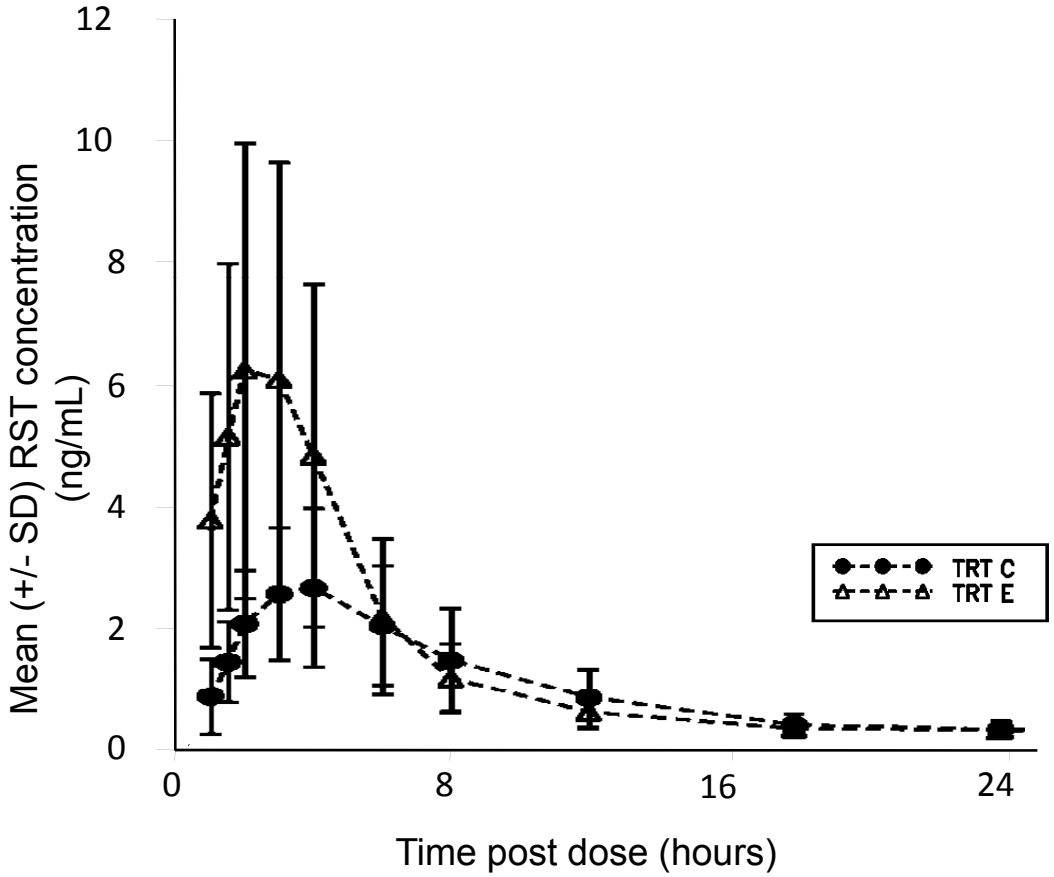
- In vitro, ASV inhibits OATP1B1, OATP2B1, and OATP1B3 with IC_{50} values of 0.3µM, 0.27µM and 3.0µM, respectively
- In vitro, ASV inhibited digoxin transport in Caco-2 cells with IC50 of 11µM but an IC50 of 50.6µM against P-gp-expressing MDCK cells
- ASV was shown to be a substrate of OATP1B1 and OATP2B1
- ASV was shown to be a substrate of P-gp in Caco-2 cells with concentration –dependent efflux ratio suggesting likely saturation at clinically relevant doses
- ASV is NOT a substrate of BCRP; IC50 >50µM

Assessment of ASV as an OATP Inhibitor

- Aim: to assess the effect of ASV on the PK of Rosuvastatin
- 20 healthy male and female subjects, ages 18-49, BMI 18-32 kg/m^2
- Single sequence crossover study design (AI447015)



ASV Increases Rosuvastatin Exposure

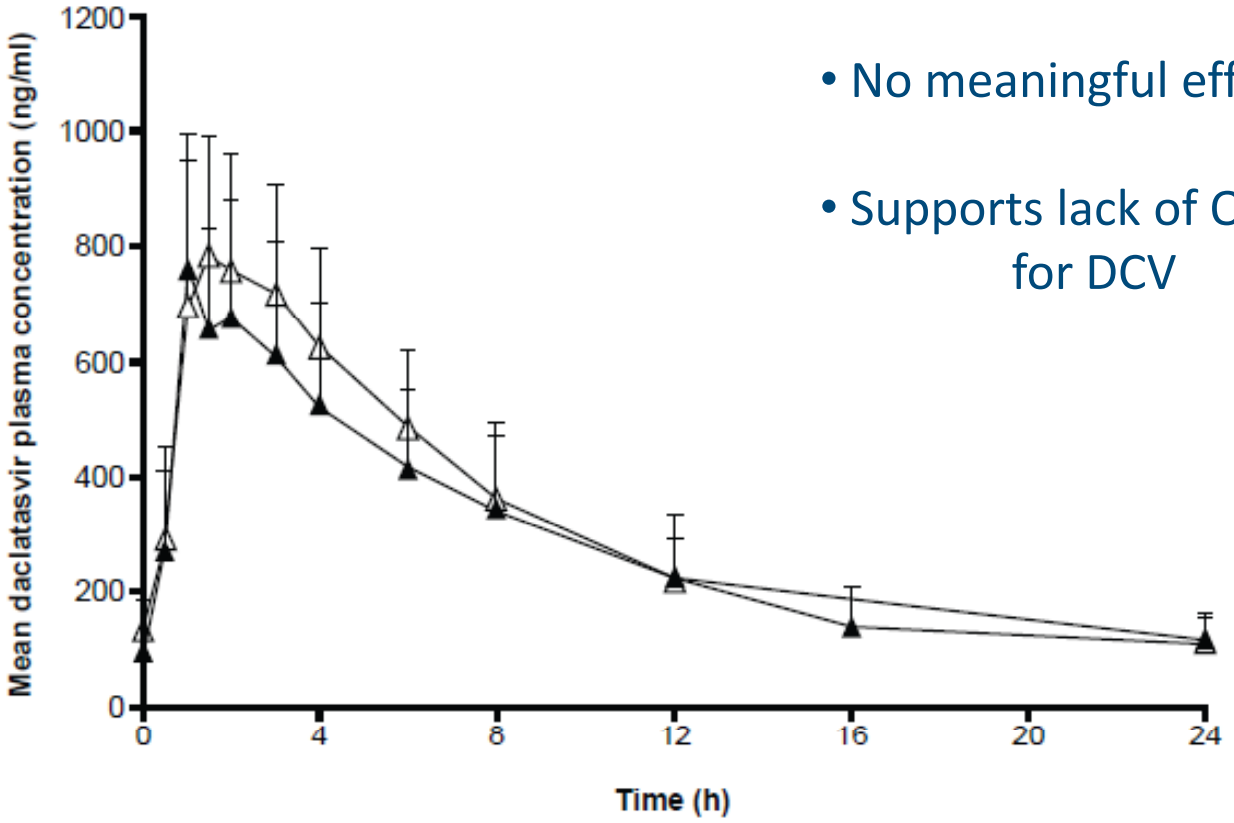


ASV effect on RST PK	
Parameter	**Geo. LSM Ratio (90 % CI)**
C_{max} (ng/mL)	1.946 (1.469-2.576)
AUC_{inf} (ng*hr/mL)	1.406 (1.257-1.573)

Weak inhibitor of OATP family, but not BCRP (based on IC50s)

LSM, least-squares mean, RST, rosuvastatin

ASV-Rosuvastatin vs. ASV-DCV Effect

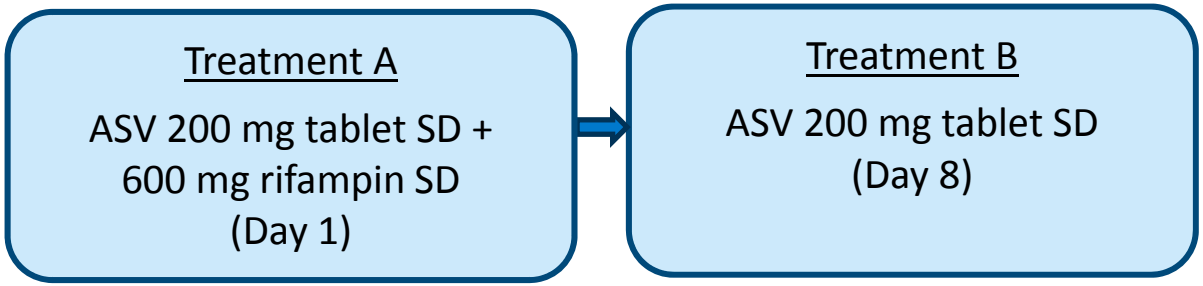


- No meaningful effect of ASV on DCV
- Supports lack of OATP-mediated uptake for DCV

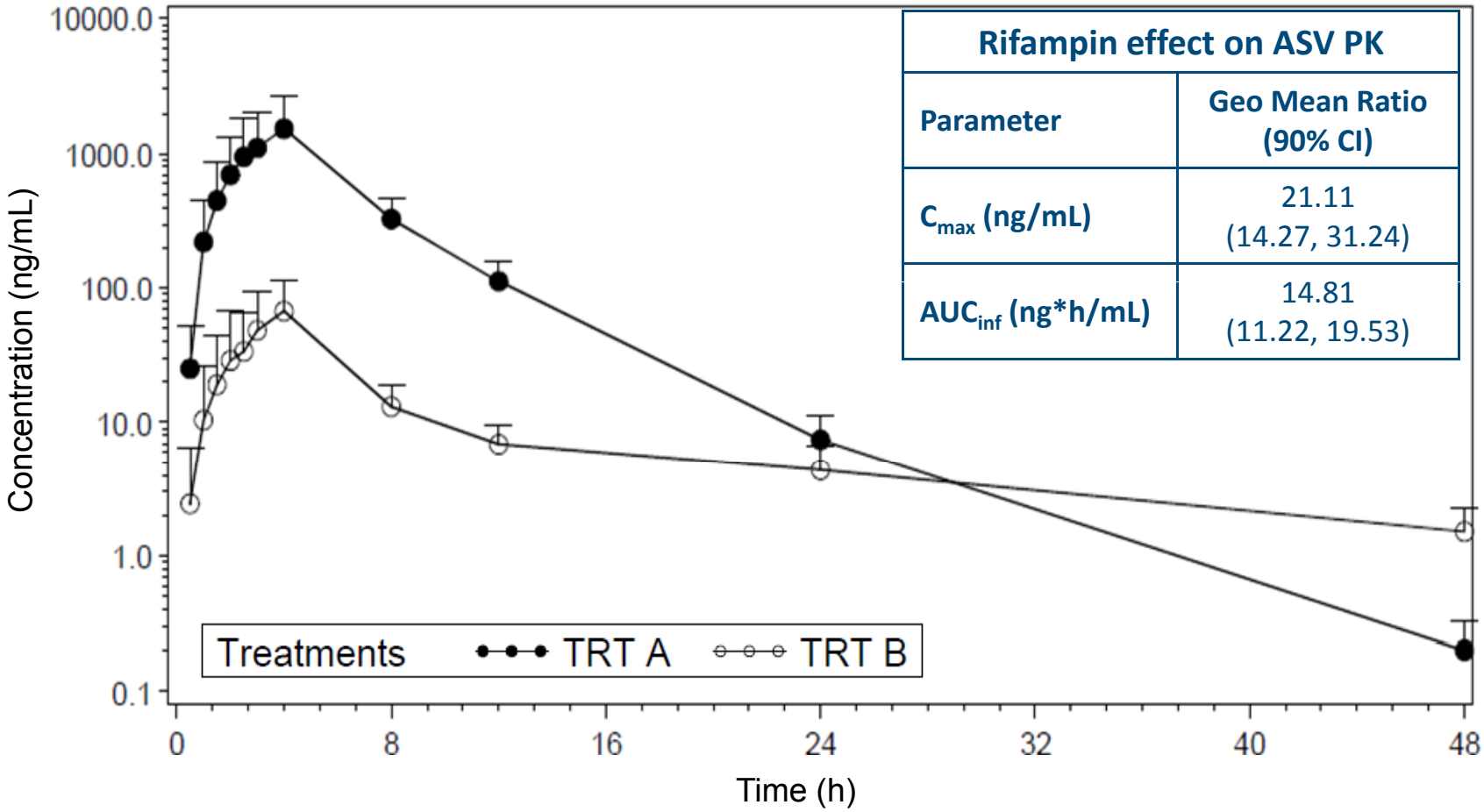
Bifano et al AASLD 2010

Assessment of ASV as an OATP Substrate

- Aim: to assess the effect of single dose rifampin on the PK of ASV
  - ASV given fasted
- 20 healthy male subjects, ages 18-49, BMI 18-30 kg/m^2
- Single sequence crossover study design (AI447018)



Rifampin Markedly Increases ASV Exposure



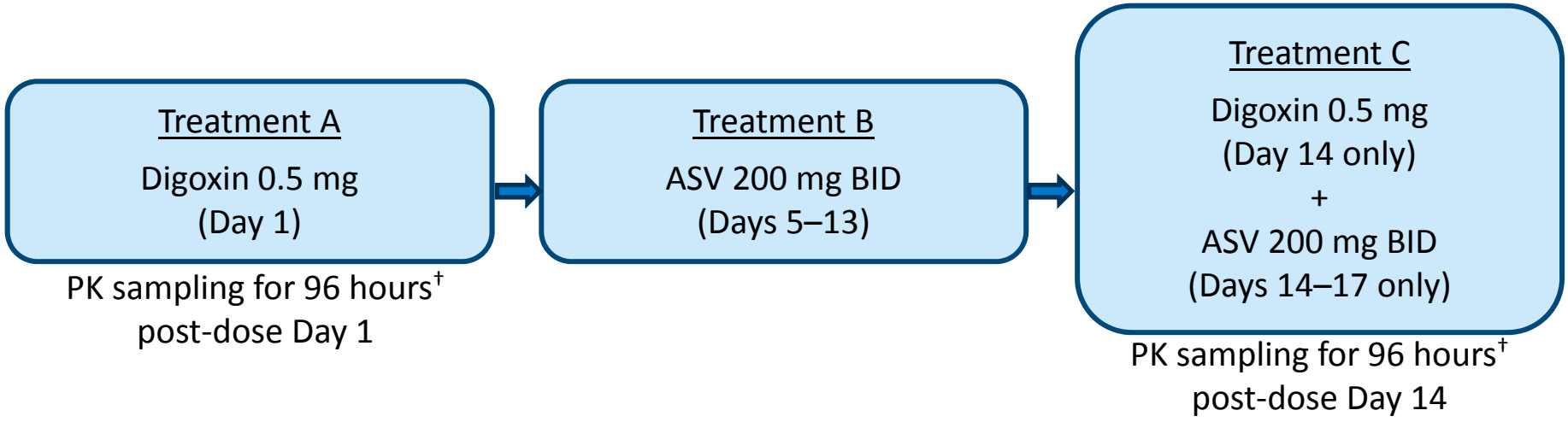
Rifampin effect on ASV PK	
Parameter	**Geo Mean Ratio (90% CI)**
C_{max} (ng/mL)	21.11 (14.27, 31.24)
AUC_{inf} (ng*h/mL)	14.81 (11.22, 19.53)

Sensitive substrate of OATP1B1 and OATP2B1

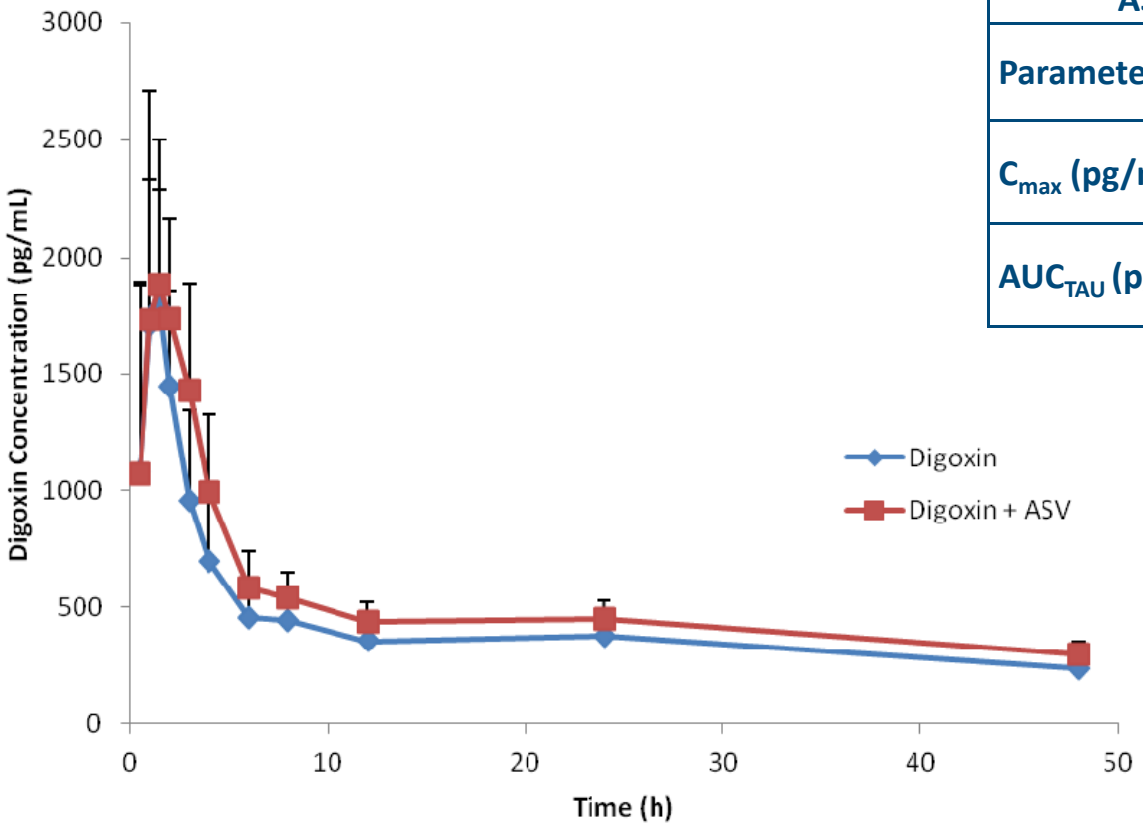
Eley et al HCV CP Workshop 2012

Assessment of ASV as a P-gp Inhibitor

- Aim: To assess the effect of ASV on the pharmacokinetics (PK) of digoxin in healthy subjects
- 16 healthy subjects, ages 18-40, BMI 18-32 kg/m^2
- Single sequence crossover study design (AI447021)



ASV Increases Digoxin Exposure



(Truncated to 48 h)

ASV effect on digoxin PK	
Parameter	Geo. Mean Ratio (90 % CI)
C_{max} (pg/mL)	1.087 (0.968,1.221)
AUC_{TAU} (pg*hr/mL)	1.303 (1.214, 1.398)

Weak P-gp inhibitor

Eley et al AASLD 2011

Clinical Implications for Asunaprevir

- ASV is a weak inhibitor of P-gp and OATPs
  - Precautionary guidance for NTI P-gp substrates likely for label
  - General precautionary statement likely for OATP substrates
- Based on available data, P-gp inhibition (in absence of CYP3A effect) unlikely to cause marked changes in ASV PK
- Strong OATP inhibitors may lower ASV hepatic concentrations
  - Prohibited in Phase 3; likely in label

Background: Daclatasvir (DCV, BMS-790052)

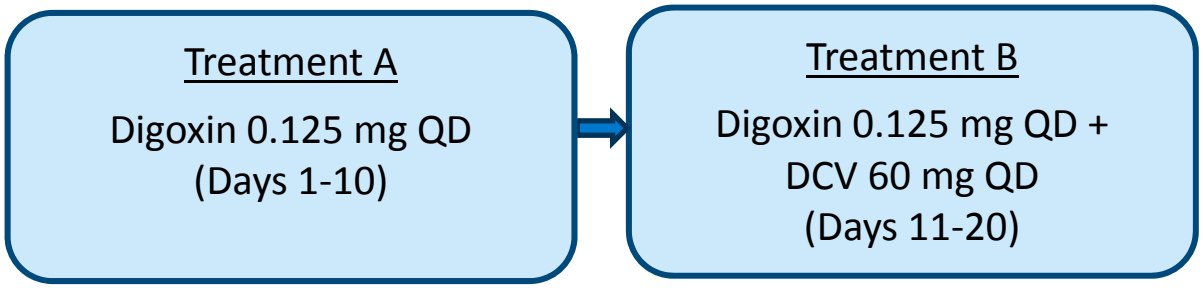
- Daclatasvir (DCV) is a potent, pan-genotypic NS5A inhibitor
  - Clinical data in GT 1, 2, 3 and 4
  - Safe and well tolerated in > 5500 patients
- Currently under FDA review as part of a combination regimen for HCV with ASV and in Phase 3 as part of an all-oral regimen with ASV and BMS-791325 as noted previously
- Geometric Mean (CV) steady state plasma C_{max} for 60 mg QD commercial tablet was 1158 ng/mL (49%) in US Phase 3 study with ASV
  - Plasma protein binding of ~99%

DCV *in vitro* Transporter Data

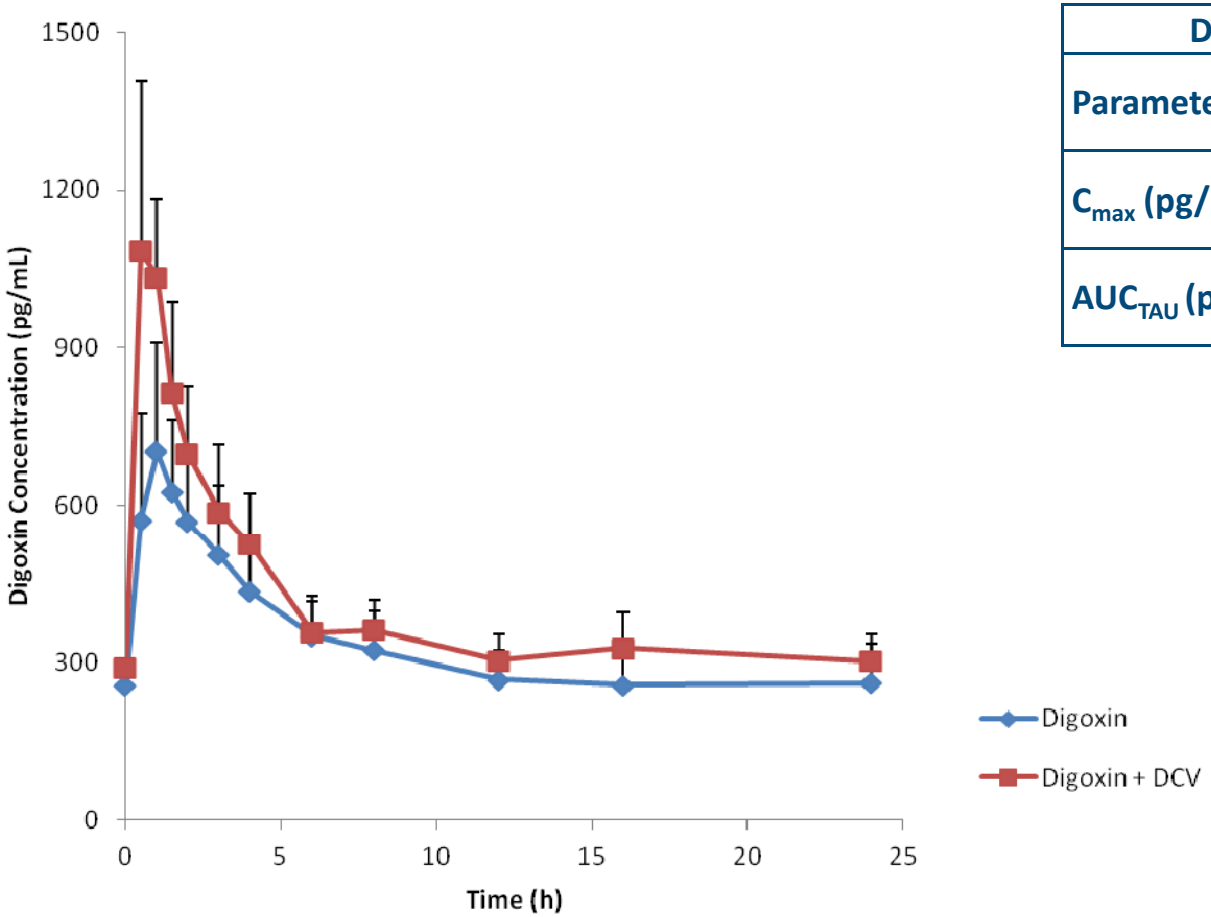
- In vitro, DCV inhibited OATP1B1, OATP2B1 and OATP1B3 with IC_{50} values of 2.3µM, 41.8µM and 5.7µM, respectively
- DCV has not been shown to be substrate of liver uptake transporters
- DCV is a P-gp inhibitor with IC50 of 4.4 µM against digoxin transport in Caco-2 cells. In P-gp-expressing MDCK cells, minimal inhibition of P-gp was observed
- DCV is a P-gp substrate based on data from Caco-2 and P-gp knockout mice
- DCV inhibits BCRP (IC50 of 10.9µM) but is NOT a BCRP substrate

Assessment of DCV as a P-gp Inhibitor

- Aim: to assess the effect of DCV on the multiple-dose PK of digoxin in healthy subjects
- 17 healthy subjects, ages 18-40, BMI 18-32 kg/m^2
- Single sequence crossover study design



DCV Increases Digoxin Exposure

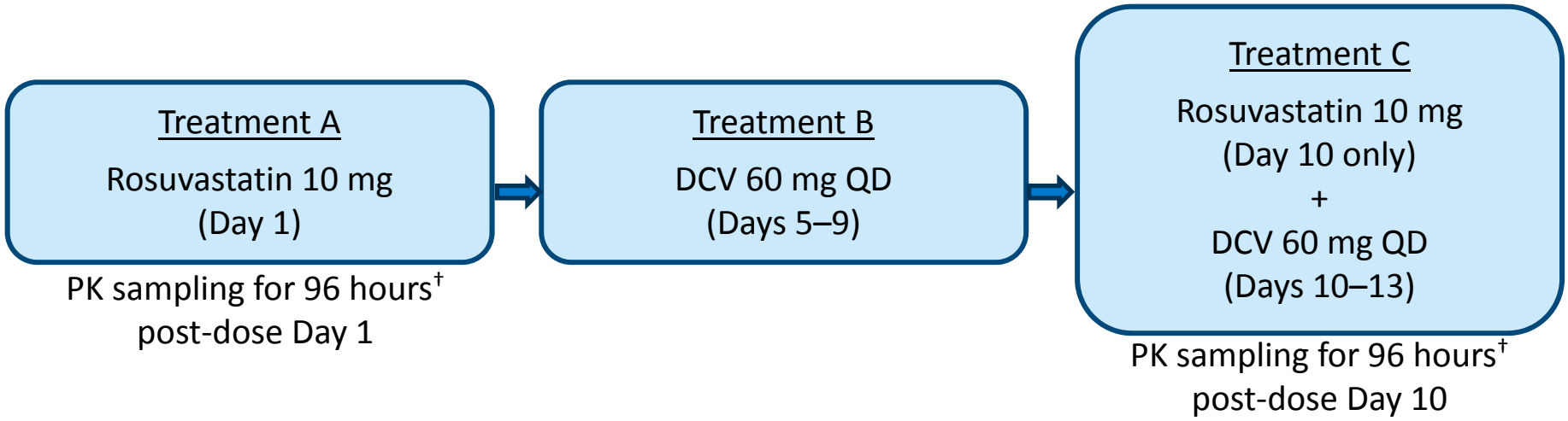


DCV effect on digoxin PK	
Parameter	**Geo. Mean Ratio (90 % CI)**
C_{max} (pg/mL)	1.65 (1.521-1.797)
AUC_{TAU} (pg*hr/mL)	1.27 (1.203-1.342)

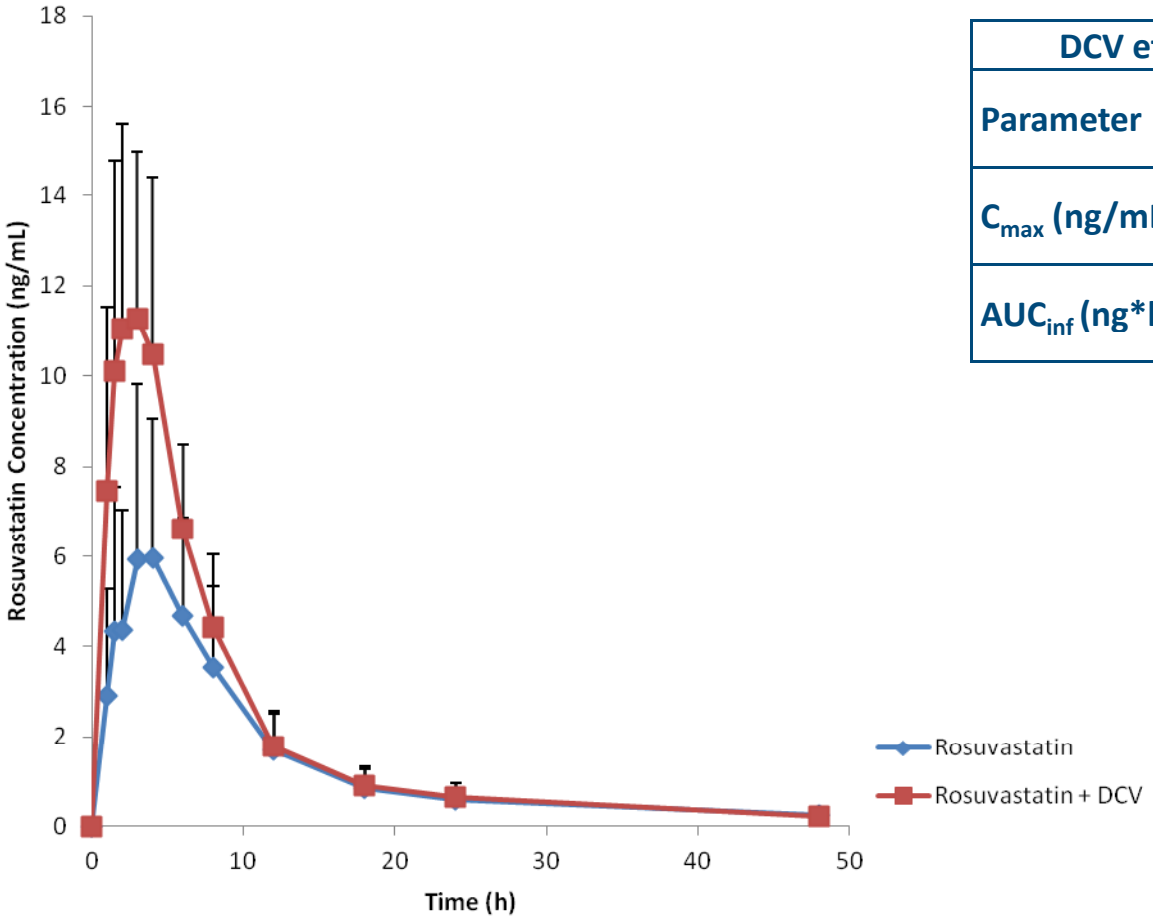
Weak to Moderate P-gp inhibitor

Assessment of DCV as an OATP Inhibitor

- Aim: to assess the effect of daclatasvir on the single-dose PK of rosuvastatin
- 22 healthy subjects, ages 18-49, BMI 18-32 kg/m^2
- Single sequence crossover study design (AI444054)



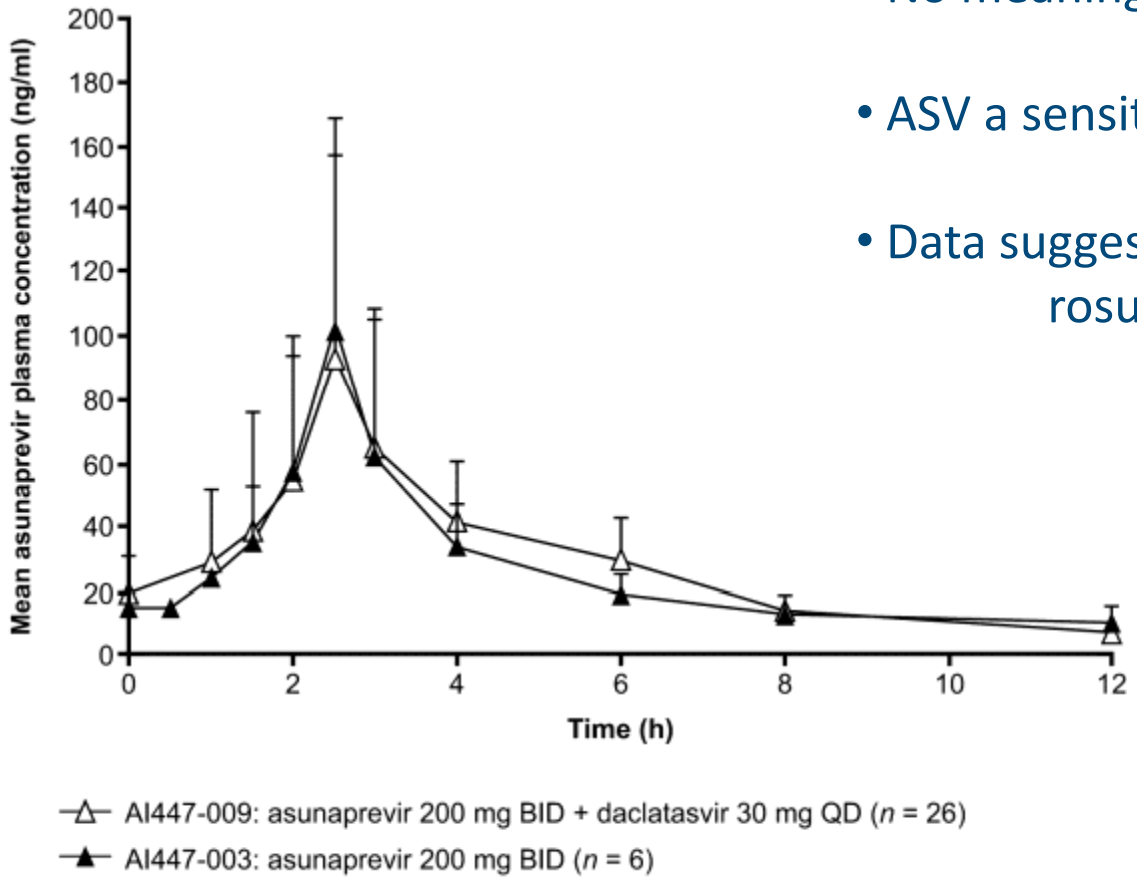
DCV Increases Rosuvastatin Exposure



DCV effect on rosuvastatin PK	
Parameter	**Geo. Mean Ratio (90 % CI)**
C_{max} (ng/mL)	2.04 (1.83-2.26)
AUC_{inf} (ng*hr/mL)	1.58 (1.44-1.74)

OATP1B1/3 inhibitor or BCRP inhibitor? Both?

DCV-Rosuvastatin vs. DCV-ASV Effect

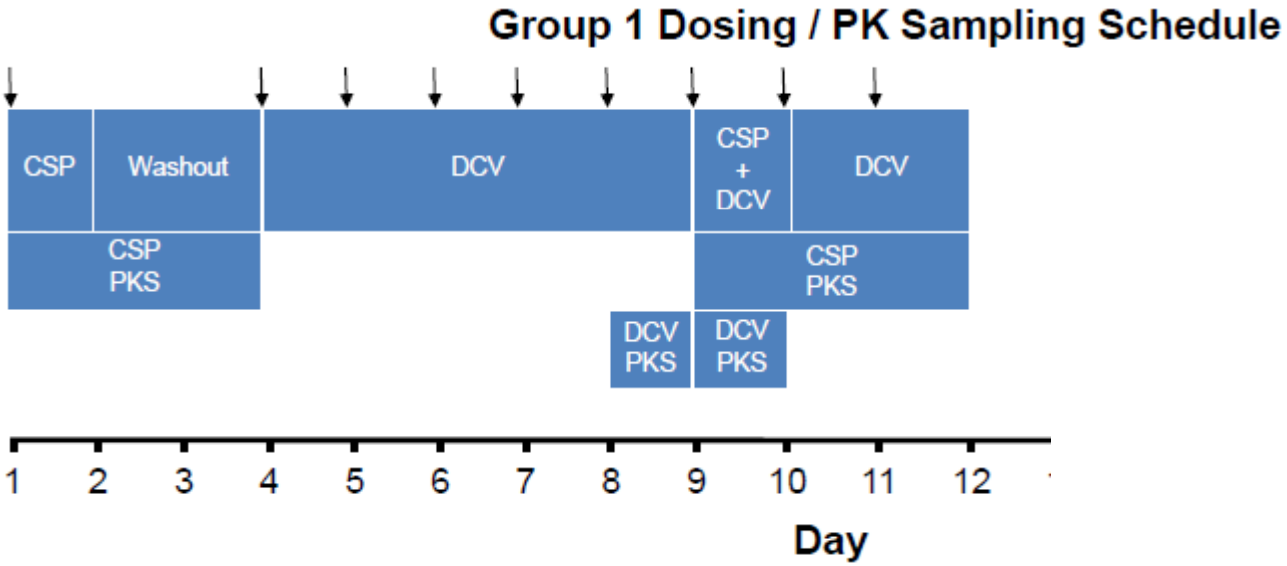


- No meaningful effect of DCV on ASV
- ASV a sensitive OATP substrate
- Data suggest BCRP inhibition by DCV in rosuvastatin study

Bifano et al AASLD 2010

Assessment of DCV as Transporter DDI Victim

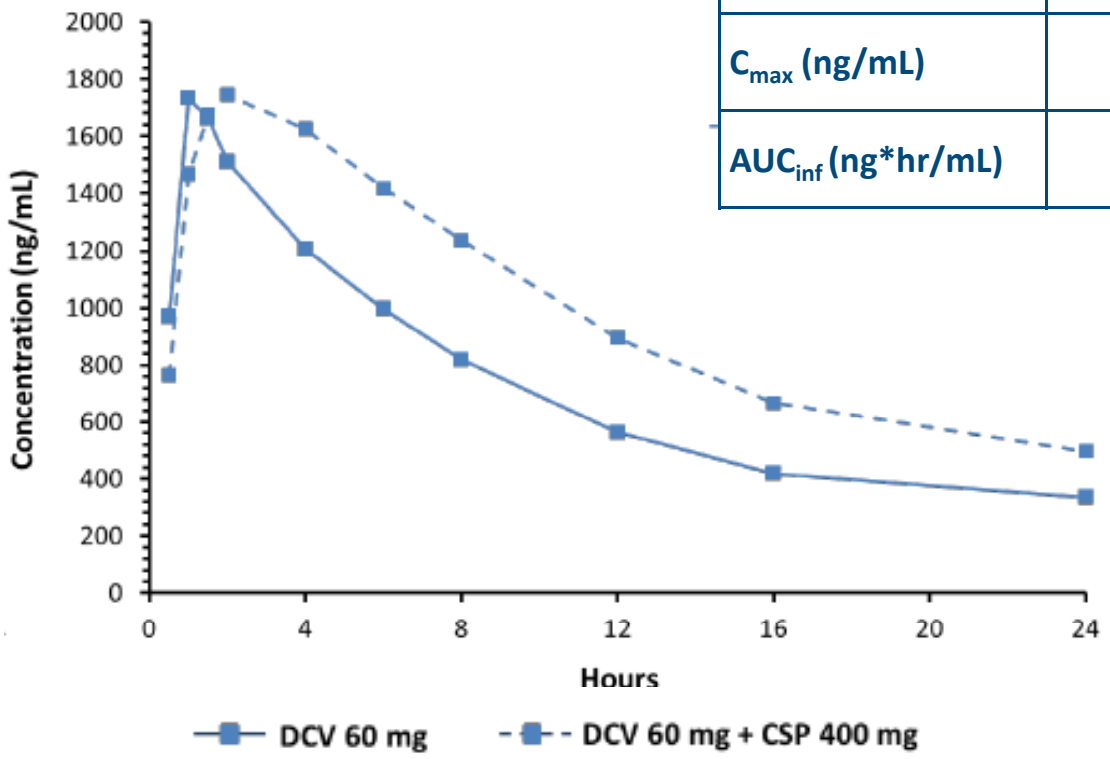
- Aim: to assess the effect of multiple doses of DCV on the single-dose PK profile of Cyclosporine (CSP) and the effect of single dose CSP on DCV PK
- 14 healthy subjects, ages 18-49, BMI 18-32 kg/m^2
- Single sequence crossover study design



Bifano et al AASLD 2013

Cyclosporine Increases DCV Exposure

Cyclosporine Effect on DCV PK	
Parameter	Geo. Mean Ratio (90 % CI)
C_{max} (ng/mL)	1.04 (0.94, 1.15)
AUC_{inf} (ng*hr/mL)	1.40 (1.29, 1.53)



- Confirms role of P-gp for DCV; other transporters unlikely
- No effect of DCV on cyclosporine (or tacrolimus)
- No effect of tacrolimus on DCV

Bifano et al AASLD 2013

Clinical Implications for Daclatasvir

- DCV is a weak/moderate inhibitor of P-gp, OATP1B1/3, BCRP
  - Precautionary guidance for NTI P-gp substrates likely for label
  - General precautionary statement likely for OATP substrates
  - General precautionary statement likely for BCRP substrates

- Based on available data, P-gp inhibition (in absence of CYP3A effect) unlikely to cause marked changes in DCV PK or need for dose adjustment

- DCV has no clinically meaningful interactions with transplant (prevention of organ rejection) medications

Summary

- ASV has limited potential to be a precipitant of transporter-based DDIs and precautionary guidance appears adequate for OATP and P-gp (NTI)
- ASV is clearly a sensitive substrate (victim) of OATP-mediated DDI and is unlikely to be co-administered with any strong OATP inhibitors
- DCV has a more favorable DDI profile in general relative to ASV and most other DAAs
  - As a precipitant of transporter-based DDIs, precautionary guidance also appears adequate for DCV with respect to P-gp (NTI) and OATP/BCRP
  - DCV has low potential to be a victim of transporter based DDI
- No clinically meaningful interaction between ASV and DCV

Acknowledgements

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Thank You