Effect of Daclatasvir/Asunaprevir/Beclabuvir in Fixed-dose Combination on the Pharmacokinetics of CYP450/Transporter Substrates In Healthy Subjects

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Disclosures

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All-Oral DCV-TRIO Regimen

- **Daclatasvir (DCV)**
  - Pangenotypic NS5A inhibitor with low DDI potential
  - Substrate of CYP3A4 and P-gp
  - Inhibitor of P-gp, OATP1B1/B3 and BCRP; inducer of CYP3A4 (weak)
- **Asunaprevir (ASV)**
  - NS3 inhibitor
  - Substrate of CYP3A4, P-gp, OATP1B1/2B1
  - Inhibitor of CYP2D6, P-gp, OATP1B1/B3; inducer of CYP3A4
- **Beclabuvir (BCV) and BMS-794712 (BCV major metabolite)**
  - Nonnucleoside NS5B inhibitor
  - Substrates of CYP3A4 and P-gp (BCV)
  - Inhibitors of P-gp , OATP1B1/B3, BCRP, NTCP, BSEP; inducer of CYP3A4
- **DCV-TRIO**
  - DCV 30 mg / ASV 200 mg / BCV 75 mg in fixed-dose combination administered twice-daily
  - High rates of sustained virologic response and generally well-tolerated in Phase 3 studies[1,2]

[1]Muir *et al*. *JAMA* 2015;313:1736-1744. [2] Poordad *et al*. *JAMA* 2015;313:1728-1735.

Study AI443021 Objective

- Assess the effect of steady-state DCV-TRIO on the PK of single-dose standard probe substrates for CYP enzymes and major human drug transporters (P-gp and OATP)[a]

CYP isozyme / transporter	Substrate	Dose, mg
CYP1A2	Caffeine	200
CYP2D6	Metoprolol	50
CYP2C8	Montelukast	10
CYP2C9	Flurbiprofen	50
CYP2C19	Omeprazole	40
CYP3A4	Midazolam	5
P-gp	Digoxin	0.25
OATP	Pravastatin	40

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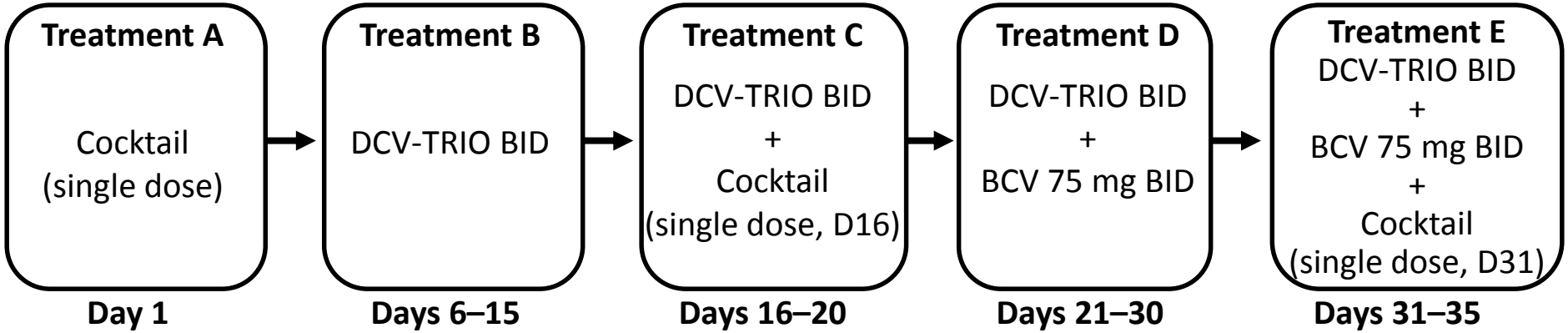
[a] Administered as a validated cocktail with no internal DDIs

Study AI443021 Design



- **Patients**: Healthy subjects aged 18–45 years; BMI 18–32 kg/m^2
- **PK blood sampling**:
  - DCV-TRIO: Pre-dose to 12 hours post-dose on Days 16 and 31
  - Probe / metabolite: Pre-dose to 120 hrs post-dose on Days 1, 16, 31
- **Analyses**: Point estimates of adjusted geometric mean ratios (GMR) and 90% confidence intervals (CIs) of C_{max} / AUC_{inf} derived from a linear mixed-effect model

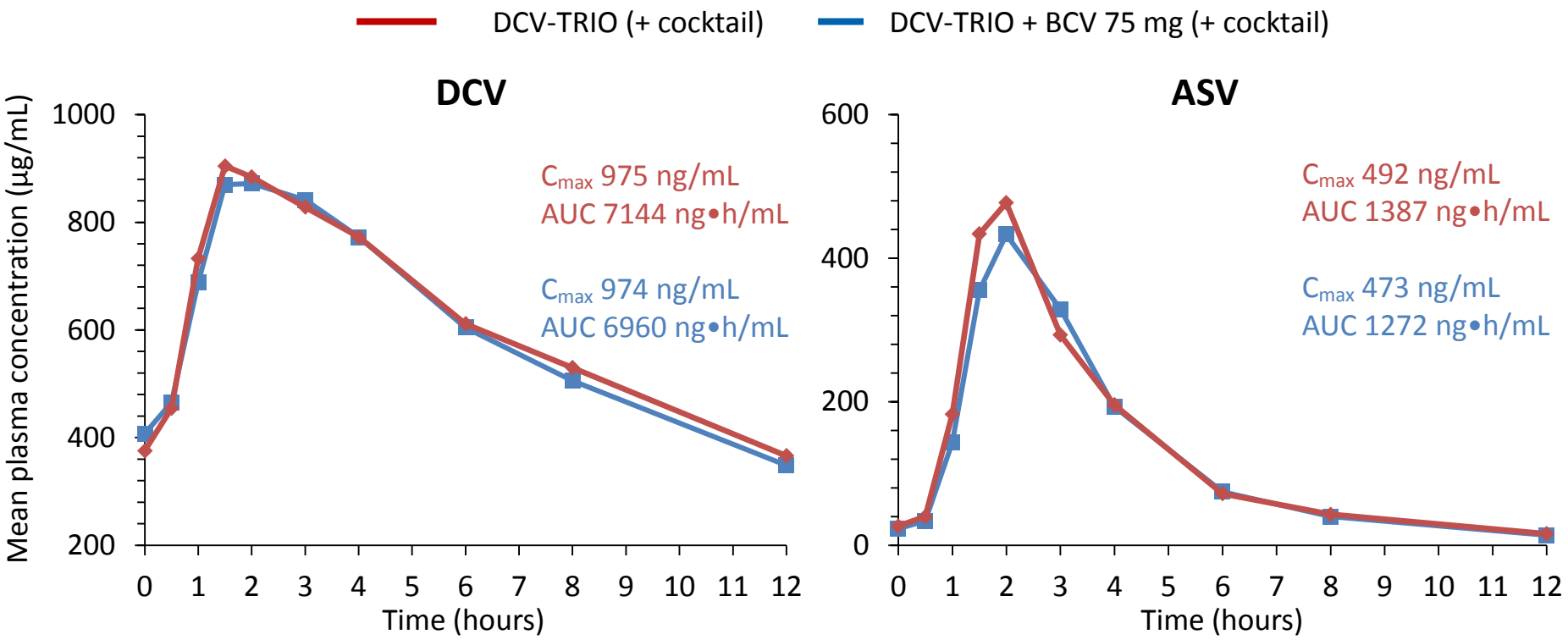
[a]Additional BCV added to account for higher BCV exposures in HCV patients relative to healthy subjects

Baseline and Demographic Characteristics

Parameter	Overall (N=20)
Age, median (range) years	31 (18–43)
Gender, n (%)	
Male	19 (95)
Female	1 (5)
Race, n (%)	
White	10 (50)
Black/African American	7 (35)
Asian	1 (5)
American Indian or Alaska Native	1 (5)
Other	1 (5)
Ethnicity, n (%)	
Hispanic/Latino	7 (35)
Not Hispanic/Latino	13 (65)
Height, median (range) cm	177 (148–191)
Weight, median (range) kg	82 (59–108)
BMI, median (range) kg/m^2	27 (19–31)

- 19/20 subjects (95%) completed the study

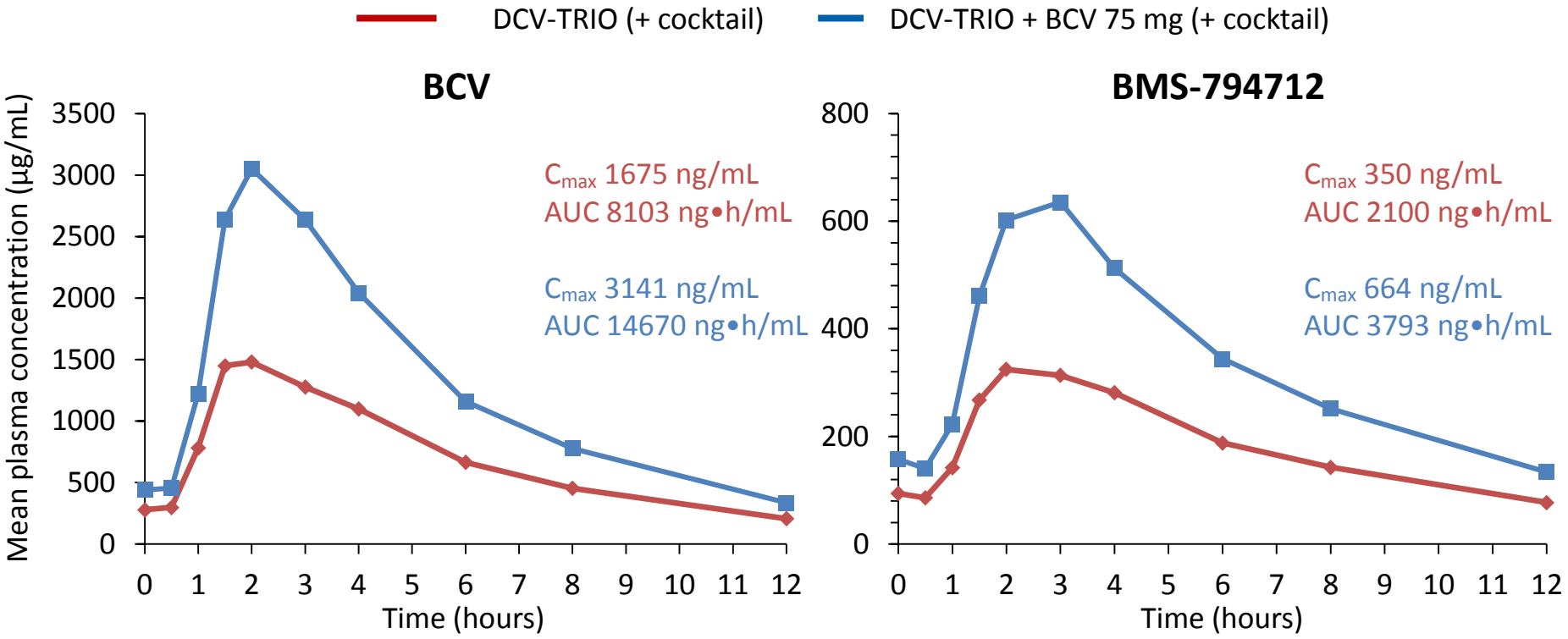
PK of DCV-TRIO Components



- DCV and ASV exposures were comparable when administered as DCV-TRIO BID and DCV-TRIO + BCV 75 mg BID (during co-administration with cocktail)
- DCV and ASV exposures during co-administration with cocktail were comparable with historic controls where DCV and ASV were administered alone or in combination[1]

[1]Eley, T *et al*. Clin Drug Investig 2014;34:661–67.

PK of DCV-TRIO Components



- Dose-proportional increases in BCV and BMS-794712 exposures were observed with additional BCV 75 mg BID (during co-administration with cocktail)
- BCV exposure following DCV-TRIO + BCV 75 mg BID was comparable with exposures observed in Phase 3 studies of DCV-TRIO (data on file)

Effect of DCV-TRIO on CYP1A2, CYP2C8 and CYP2C9

Caffeine (CYP1A2)

C_{max} 0.97 (0.93–1.02)

AUC_{inf} 0.96 (0.90–1.01)

Montelukast (CYP2C8)

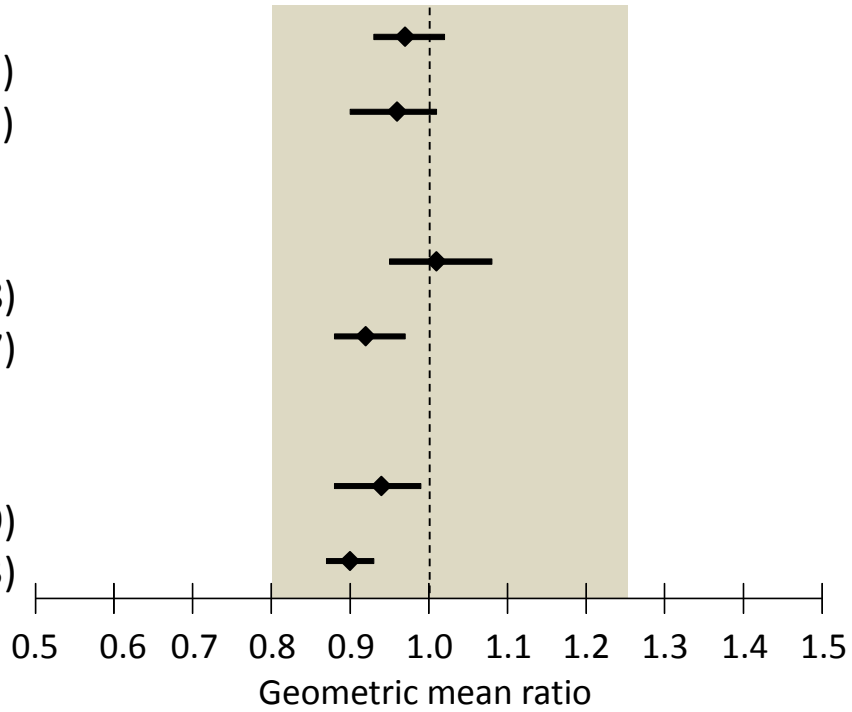
C_{max} 1.01 (0.95–1.08)

AUC_{inf} 0.92 (0.88–0.97)

Flurbiprofen (CYP2C9)

C_{max} 0.94 (0.88–0.99)

AUC_{inf} 0.90 (0.87–0.93)



- DCV-TRIO BID had no clinically-meaningful effect on CYP1A2, CYP2C8 or CYP2C9
  - GMRs and 90% CIs of probe substrates were contained within the range of bioequivalence (0.80–1.25)
  - Additional BCV 75 mg BID had no further meaningful effect (data not shown)

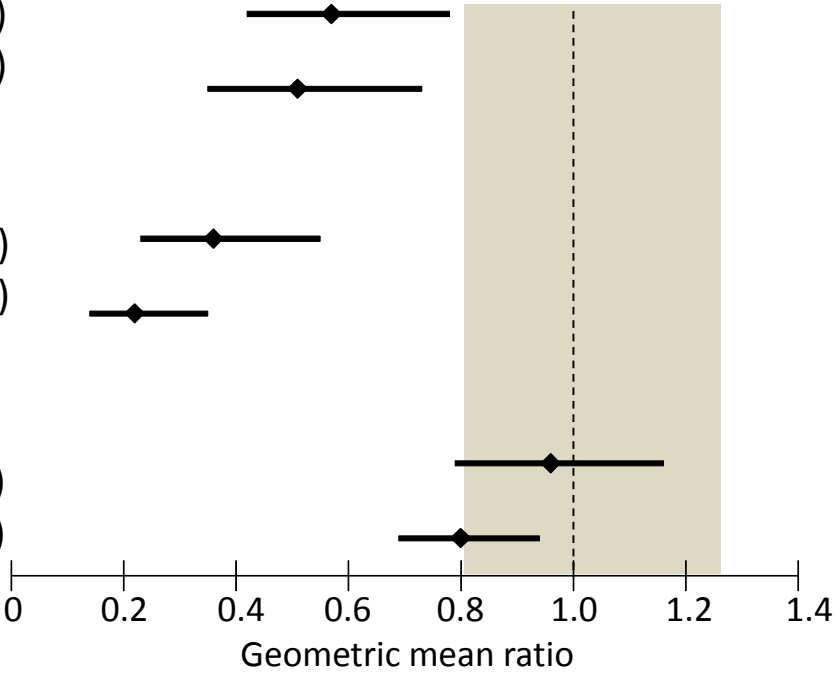
Shaded area represents the accepted range of bioequivalence (0.8–1.25)

Effect of DCV-TRIO on CYP2C19

DCV-TRIO
Omeprazole
C_{max} 0.57 (0.42–0.78)
$AUC_{0–T}$ 0.51 (0.35–0.73)

DCV-TRIO + BCV 75 mg
Omeprazole
C_{max} 0.36 (0.23–0.55)
$AUC_{0–T}$ 0.22 (0.14–0.35)

ASV 200 mg BID alone[1]
Omeprazole
C_{max} 0.96 (0.79–1.16)
AUC_{inf} 0.80 (0.69–0.94)

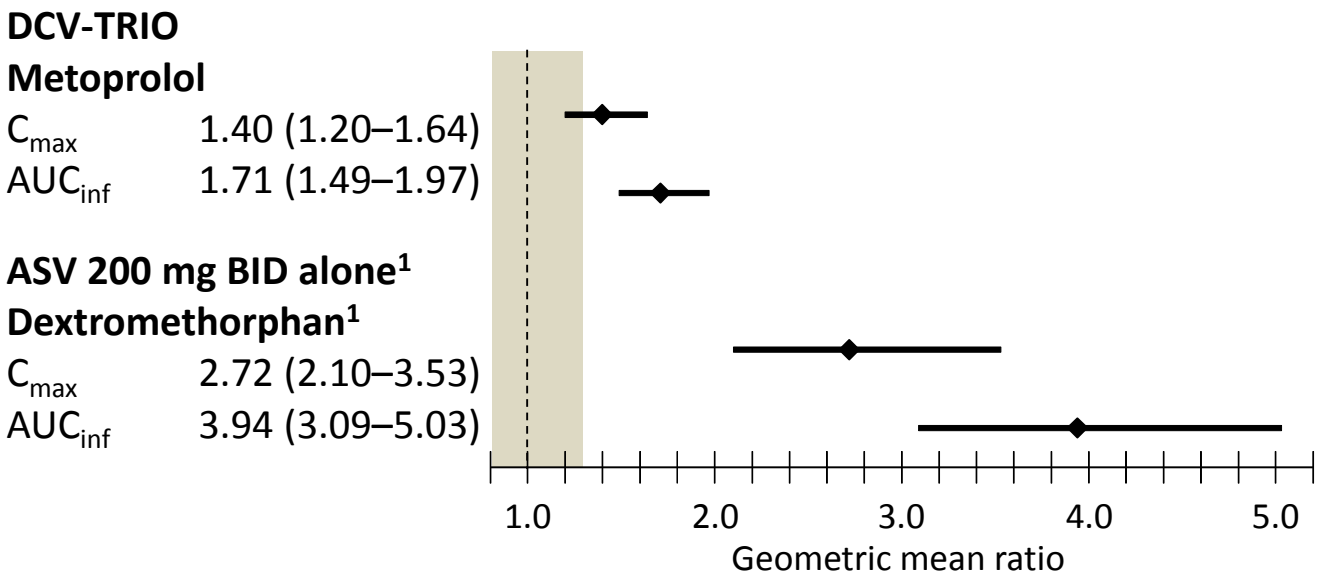


- DCV-TRIO BID caused weak-to-moderate induction of CYP2C19
  - Omeprazole C_{max} and $AUC_{0–T}$ decreased by 43% and 52%, respectively, during co-administration
- DCV-TRIO + BCV 75 mg BID caused moderate induction of CYP2C19
  - Omeprazole C_{max} and $AUC_{0–T}$ decreased by 40% and 66%, respectively

CYP2C19 poor metabolisers (n=2) were excluded from the analyses
Shaded area represents the accepted range of bioequivalence (0.8–1.25)

[1] Eley T *et al*. Clinical Pharmacokinet 2015;54:1205–22.

Effect of DCV-TRIO on CYP2D6



- DCV-TRIO BID caused weak-to-moderate inhibition of CYP2D6
  - Metoprolol C_{max} and AUC_{inf} increased by 40% and 71%, respectively during co-administration
  - Additional BCV 75 mg BID had no further meaningful effect (data not shown)
- Impact of DCV-TRIO BID on the PK of metoprolol was less than the effect of ASV 200 mg BID alone at steady-state on the PK of single-dose dextromethorphan (CYP2D6 substrate)[1]

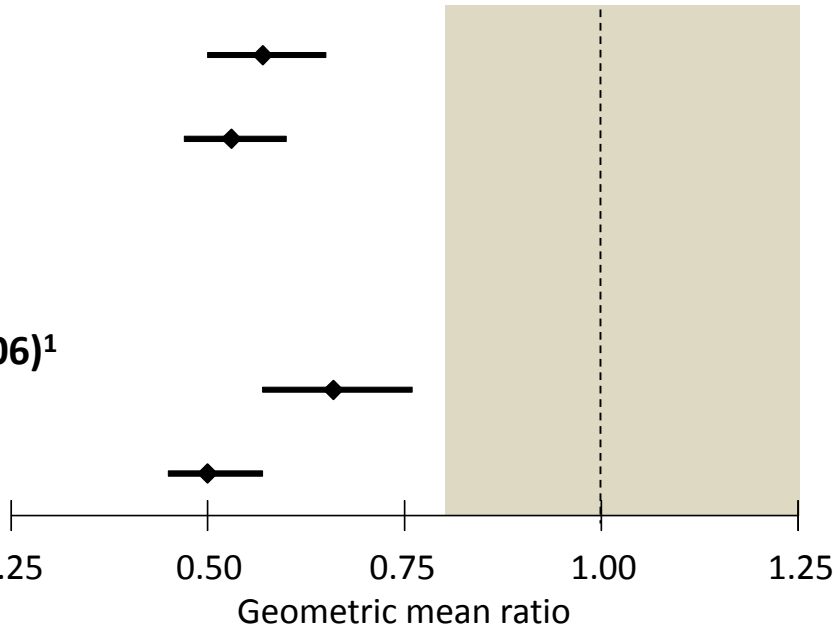
No CYP2D6 poor metabolisers were included in the current analyses;
Shaded area represents the accepted range of bioequivalence (0.8–1.25)

[1] Eley T *et al*. Clinical Pharmacokinet 2015;54:1205–22.

Effect of DCV-TRIO on CYP3A4

DCV-TRIO
Midazolam
C_{max} 0.57 (0.50–0.65)
AUC_{inf} 0.53 (0.47–0.60)

BCV 150 mg alone
Midazolam (Study AI443-006)[1]
C_{max} 0.66 (0.57–0.76)
AUC_{inf} 0.50 (0.45–0.57)

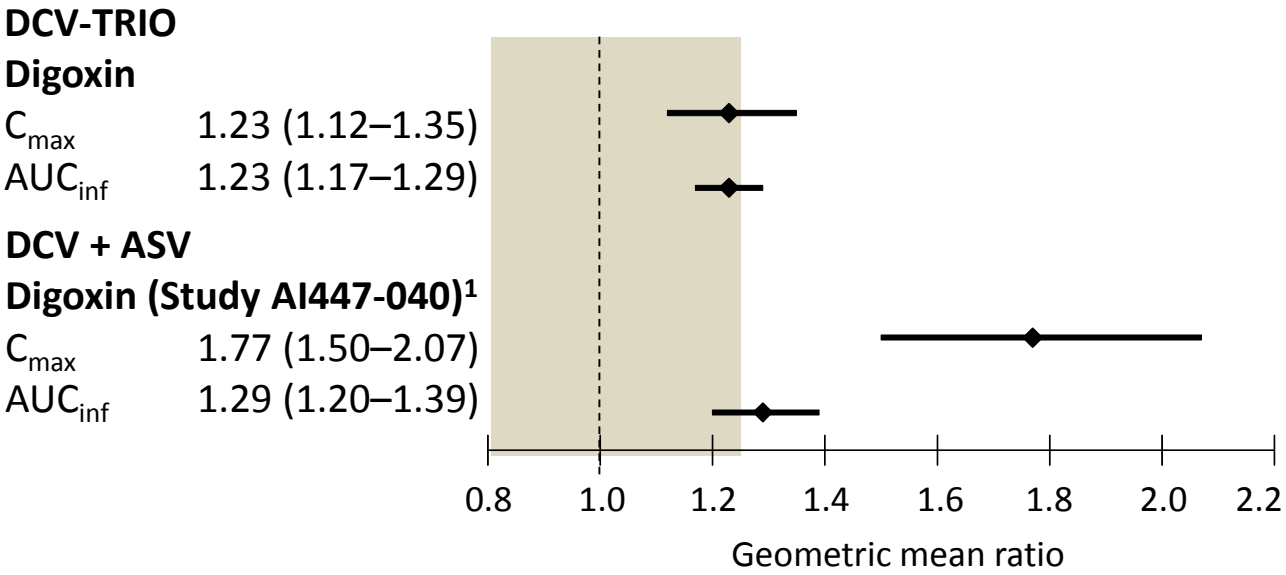


- DCV-TRIO caused weak to moderate induction of CYP3A4
  - Midazolam C_{max} and AUC_{inf} decreased by 43% and 47%, respectively, during co-administration
  - Additional BCV 75 mg BID had no further meaningful effect (data not shown)
  - No additional impact from DCV / ASV was observed
  - Degree of impact was comparable to the effect of steady-state BCV 150 mg alone (Study AI443-006)

Shaded area represents the accepted range of bioequivalence (0.8–1.25)

[1] AbuTarif M *et al*. 15th Int. Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy, 2014: Poster PP_22.

Effect of DCV-TRIO on P-gp

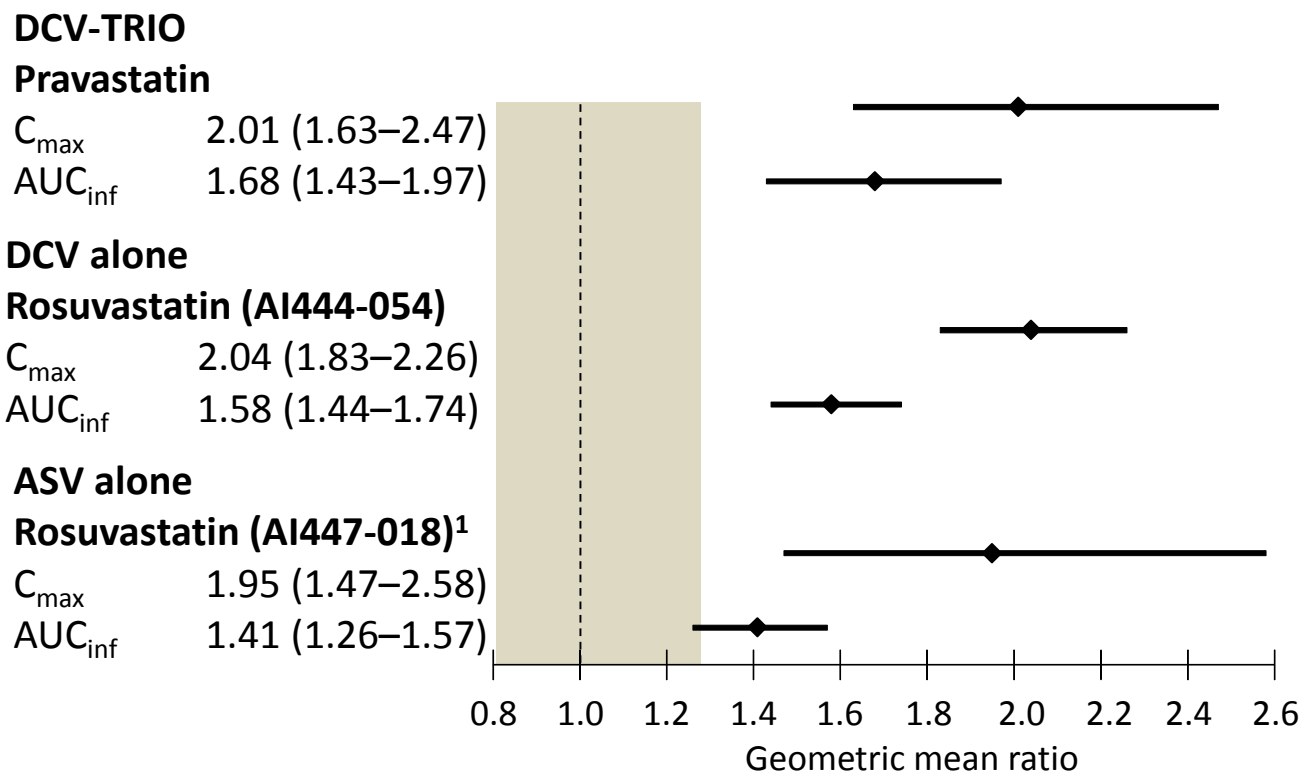


- DCV-TRIO BID caused weak inhibition of P-gp
  - Digoxin C_{max} and AUC_{inf} both increased by 23% during co-administration
  - Additional BCV 75 mg BID had no further meaningful effect (data not shown)
  - Degree of impact on P-gp was comparable to that of DCV + ASV alone (Study AI447-040)[1]

Shaded area represents the accepted range of bioequivalence (0.8–1.25)

[1] Garimella T *et al*. Infectious Disease Week, 2014: Poster 822.

Effect of DCV-TRIO on OATP



- DCV-TRIO BID inhibited OATP
  - Pravastatin C_{max} and AUC_{inf} increased by 101% and 68%, respectively during co-administration
  - Additional BCV 75 mg BID had no further meaningful effect (AUC increased by a further 13%)
  - Effect of DCV-TRIO was comparable to that of DCV or ASV administered alone (using rosuvastatin as OATP probe)

Shaded area represents the accepted range of bioequivalence (0.8–1.25)

[1] Eley T *et al*. Clinical Pharmacokinet 2015;54:1205–22.

Safety

- There were no deaths or serious adverse events
- One subject discontinued due to and AE (hemorrhoidal hemorrhage related to flurbiprofen)
- The most frequent AEs were constipation, nausea, and dizziness
  (all reported by three subjects each)
- All AEs were mild or moderate in intensity and resolved during the study
- No clinically significant changes in urinalysis, blood chemistry, electrocardiogram readings or vital signs were observed

Summary

- **DCV-TRIO has no effect on CYP1A2, 2C8, or 2C9**
- **DCV-TRIO is a moderate inducer of CYP2C19**
  - Induction of CYP2C19 was BCV dose-dependent
- **DCV-TRIO is a weak-to-moderate inhibitor of CYP2D6**
  - Impact of DCV-TRIO on exposure of metoprolol was less than the effect of ASV alone on the exposure of dextromethorphan
- **DCV-TRIO is a weak-to-moderate inducer of CYP3A4**
  - Comparable levels of induction were observed with BCV 150 mg alone, indicating no additive or synergistic effect on CYP3A4 induction when DCV, ASV and BCV are co-administered
- **DCV-TRIO is a weak inhibitor of P-gp**
  - P-gp inhibition by DCV-TRIO was comparable to that of DCV + ASV alone and indicates no additive / synergistic inhibition with the addition of BCV
- **DCV-TRIO is a weak-to-moderate inhibitor of OATP**
  - Inhibition of OATP was slightly higher with DCV-TRIO

Conclusions

- No dose adjustments are required during co-administration of DCV-TRIO FDC with substrates of CYP1A2, CYP2C9, CYP2C8, or P-gp
- Co-administration of DCV-TRIO FDC with substrates of CYP3A4, CYP2D6 or OATP should be approached with caution
- Co-administration of DCV-TRIO with drugs solely eliminated by CYP2C19 is not recommended