Clinical Pharmacology update on the direct acting antivirals faldaprevir and BI 207127

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Boehringer Ingelheim

Presenter disclosure

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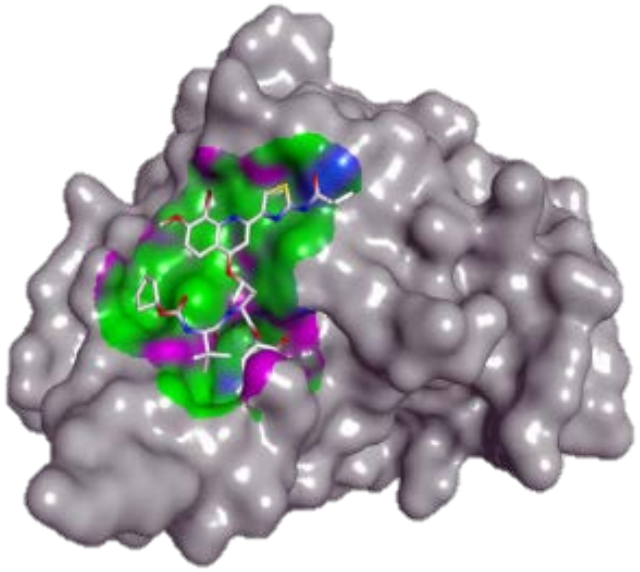
I am an employee of
Boehringer Ingelheim Pharmaceuticals, Inc.

AND

My presentation includes information on faldaprevir and BI 207127 which are investigational compounds and not yet approved

Introduction to faldaprevir



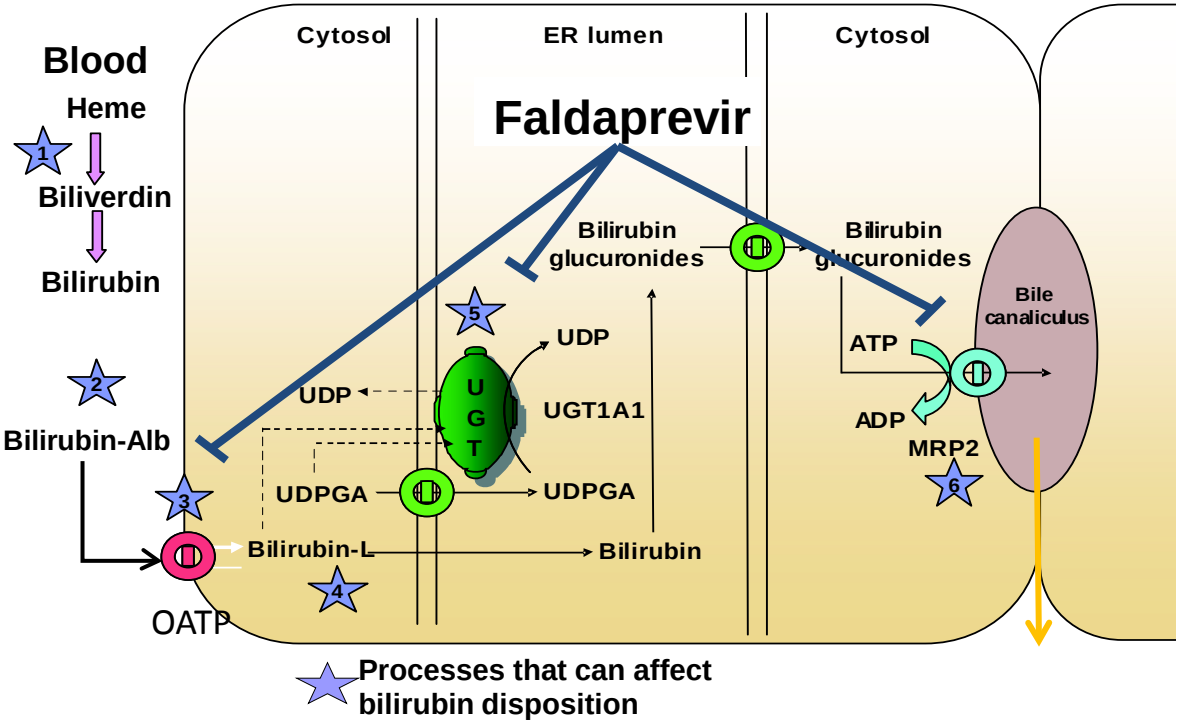
Faldaprevir-NS3/4A protease interaction
Green = hydrophobic
Blue = mildly polar
Purple = H bonding

- Faldaprevir (FDV) is a potent and selective inhibitor of the HCV NS3/A4 protease, with high *in vitro* activity in HCV genotypes (GT) 1,2, 4, 5 and 6
- The pharmacokinetics of FDV allow oral once daily administration
- Phase II data demonstrated potent antiviral activity against HCV GT1, either with pegylated infereron and ribavirin or in an interferon-free combination with BI 207127 and RBV
- Both FDV programs are currently in Phase III development

Llinàs-Brunet M, et al. J Med Chem 2010;53:6466–6476;
Sulkowski M, et al. Hepatology 2013 [Epub ahead of print]
Zeuzem S, et al. Gastroenterology 2011;141:2047–2055

Faldaprevir metabolism and bilirubin disposition

- FDV is a substrate and inhibitor of CYP3A4
- FDV is a substrate of OATP1B1and possible inhibitor of OATP1B1, OATP1B3 and OATP2B1
- FDV is a substrate of hepatic and intestinal efflux transporters P-gp and MRP2
- FDV is an inhibitor of UGT1A1
- FDV is associated with hyper-bilirubinemia, largely due to unconjugated bilirubin and completely reversible after FDV treatment is stopped



Sane R, et al. J Hepatol 2011;54(Suppl. 1):S488
Sabo JP, et al., ICACC 2012, Abstract A1248

Faldaprevir trough plasma concentrations in HCV-infected patients and healthy volunteers

Steady-state trough at week 4 of dosing	HCV-infected patients			Healthy volunteers
	FDV 120mg QD+ PegIFN/RBV n=55	FDV 240mg QD+ PegIFN/RBV n=119	FDV 240 mg BID + PegIFN/RBV n=42	FDV 240 mg BID n=23
Mean relative troughs, compared to reference	Reference 100%	approximately 450%	approximately 2700%	approximately 860%

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Faldaprevir pharmacokinetics in patients with and without compensated cirrhosis (CPA)

PK parameter (steady state), Reference Mean (%CV)	Treatment-experienced FDV 240 mg QD + PegIFN/RBV	
	No Cirrhosis n=15	Cirrhosis n=6
C_{max} (ng/mL)	Reference 100% (68.6)	106% (117)
C_{min} (ng/mL)	Reference 100% (85.6)	106% (86.8)
$AUC_{0-\tau}$(ng·h/mL)	Reference 100% (66.3)	108% (79.7)
$t_{1/2}$(h)	20.5 (26.3)	23.8 (35.1)

With 240mg QD, FDV PK parameters appeared to be similar for patients without cirrhosis and with compensated cirrhosis

Boehringer Ingelheim. Data on file

Faldaprevir clinical drug interactions

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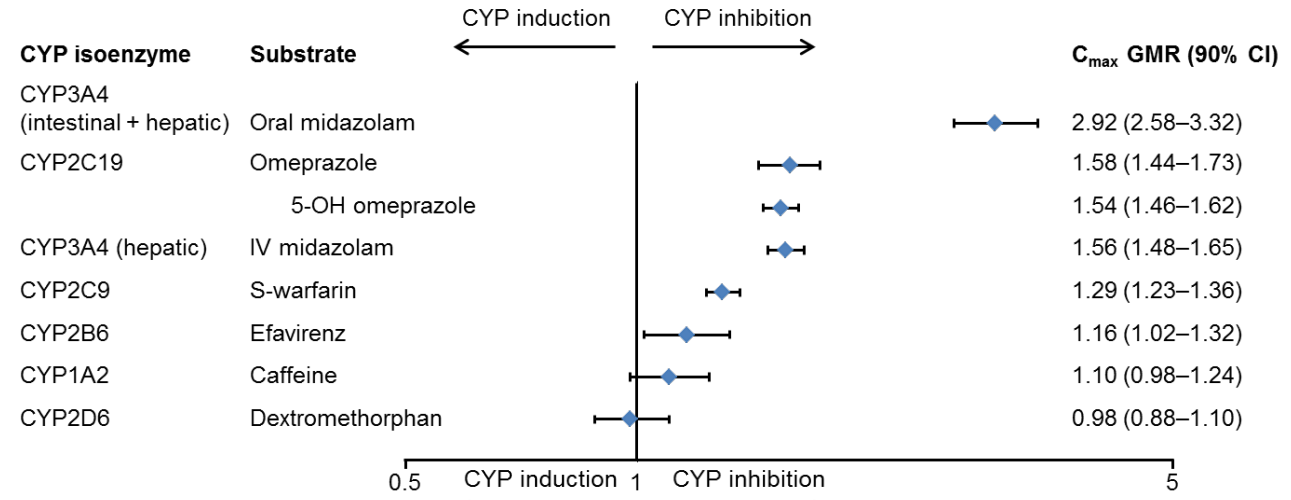
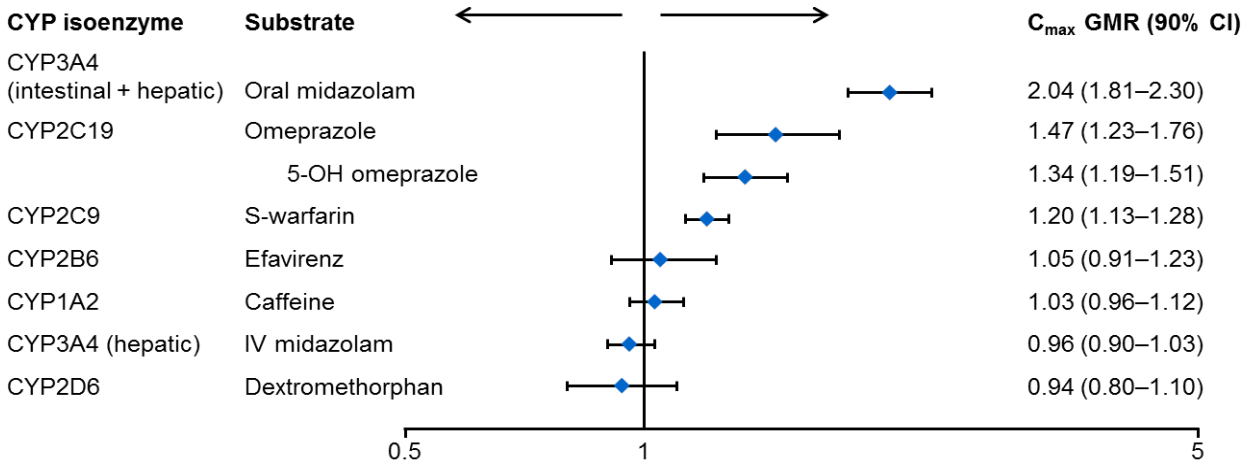
Effect of FDV on CYP probe substrate AUC



Effect of FDV on CYP probe substrate C_{max}



A geometric means ratio of 1 indicates no change

- FDV showed moderate inhibition of hepatic CYP3A4 and weak inhibition of CYP2C9
- FDV had no relevant effect on CYP2B6, CYP1A2, CYP2C19 or CYP2D6

Sabo J, et al. ICAAC 2012. Poster A-1248

Effect of Faldaprevir 120mg QD on CYP3A4 and CYP2C9 in HCV-infected patients

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Rationale:

- Faldaprevir exposure in HCV patients with 240mg QD dosage is approximately 4 to 5 fold higher when compared to the exposure with 120mg QD

- The magnitude of in vivo Faldaprevir inhibition of CYP3A4 and CYP2C9 is likely dependent on FDV exposure

- Modeling predicts weak CYP3A4 inhibition and no relevant effect on CYP with 120mg QD Faldaprevir in patients which is less than the observed moderate inhibition of CYP3A4 and weak inhibition of CYP2C9 in healthy volunteers, and at a faldaprevir exposure is approximately 2-fold higher when compared to the faldaprevir exposure with 240mg QD dosage in HCV patients.

- *The study has been completed, and results will be reported later this year*

Faldaprevir interactions with antiretrovirals

- Darunavir/Ritonavir 800mg/100mg QD
- Efavirenz 600mg QD, or 50 mg
- Tenofovir, 300mg TDF QD

Effect of Faldaprevir on Antiretrovirals

Treatment		GMR (90% CI)		
	N	C_{max}	AUC	C_{min}
DRV/r + FDV	14	1.28 (1.16–1.43)	1.15 (1.01–1.31)	0.88 (0.69–1.13)
TFV + FDV	16	0.95 (0.85–1.05)	1.22 (1.12–1.33)	1.47 (1.35–1.61)
EFV_{50} +FDV	14	1.05 (0.91-1.23)	1.16 (1.02-1.32)	--.--

Sabo et al., ICAAC 2012, Sabo et al., CROI 2013

Effects of Antivirals on Faldaprevir

Treatment		gMean		
	N	C_{max} (ng/mL)	AUC (ng·h/mL)	C_{min} (ng/mL)
FDV+ DRV/r[a]	14	8780	115000	2660
FDV alone[a]	5	5360	50100	695
% Change in FDV with DRV/r		↑64%	↑129%	↑283%

[a]Baseline ss FDV PK parameters derived from male volunteers in study 1220.06 (n=5); ssFDV+DRV/r PK parameter derived from study 1220.49 in healthy volunteers

Treatment		GMR (90% CI)		
	N	C_{max}	AUC	C_{min}
FDV + EFV + MDZ[a]	15[b]	0.72 (0.61–0.84)	0.65 (0.53–0.79)	0.54 (0.40–0.73)
FDV + TFV	16[b]	0.82 (0.72–0.93)	0.78 (0.71–0.85)	0.75 (0.69–0.83)

[a]MDZ was co-administered as a probe substrate.
[b]n=14 for FDV + EFV + MDZ, n=15 for FDV alone. [c]n=16 for FDV + TFV, n=14 for FDV alone

Sabo et al., ICAAC 2012, Sabo et al., CROI 2013

Effect of Faldaprevir on oral contraceptives: Results of Phase I study in healthy Women OCBP

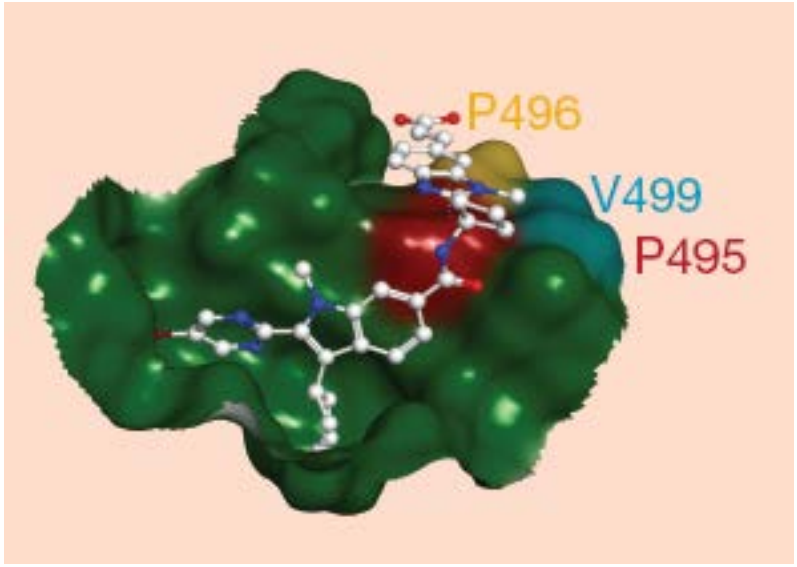
Treatment		GMR (90% CI)		
	N	C_{max}	AUC	C_{min}
FDV + EE	15[b]	1.15 (1.05-1.25)	1.41 (1.338-1.48)	1.71 (1.60-1.83)
FDV + LNG	15[b]	1.15 (1.10–1.19)	1.40 (1.36–1.44)	1.54 (1.46–1.62)

EE Ethinylestradiol 30 µg
LNG Levonorgestrel 150 µg

Faldaprevir treatment resulted in modest increases of each component of combination oral contraceptive treatment

Boehringer Ingelheim. Data on file

Introduction to the faldaprevir/BI 207127/RBV iFree regimen



BI 207127-NS5B polymerase interaction

- BI 207127 is a potent and selective non-nucleoside inhibitor of the HCV NS5B polymerase
- The pharmacokinetics of BI 207127 support BID and TID dosing
- In Phase II studies, the combination of BI 207127, FDV and RBV achieved high SVR rates in patients with GT1b, and lower SVR rates in GT1a patients
- This iFree regimen is in Phase III development

Beaulieu PL, et al. J Hepatol 2009;56:S321
Zeuzem S, et al. Manuscript in preparation

BI 207127 Metabolism

- Two major metabolites of BI 207127 were identified in humans:
  - CD 6168 (alkene reduction of BI 207127):
    ~32% of BI 207127 related material in plasma
  - BI 208333 (acyl glucuronide of BI 207127):
    ~23% of BI 207127 related material in plasma
- CD 6168 is formed in the gastrointestinal tract by gut bacteria
- BI 208333 is formed by UGT1A1, 1A3, 1A7 and 1A8
  - UGT1A1 contribution appears to be predominant
- BI 207127 is a substrate of hepatic uptake transporters OATP1B1 and OATP1B3
- BI 207127 is also a substrate of hepatic and intestinal efflux transporters P-gp and BCRP

Boehringer Ingelheim. Data on file

PK profile of faldaprevir and BI 207127

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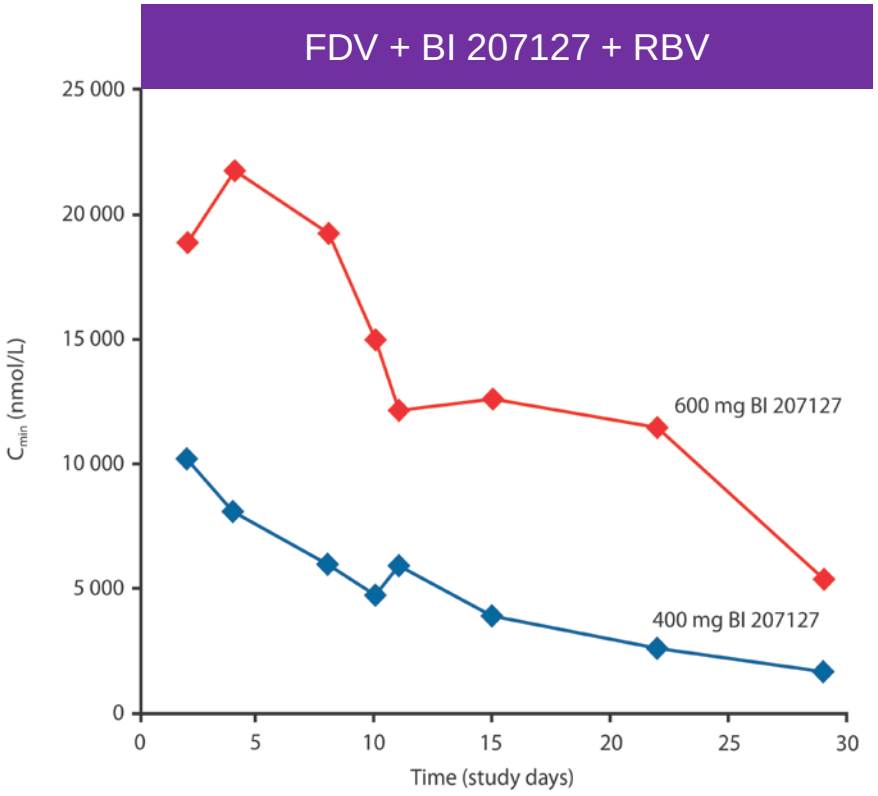
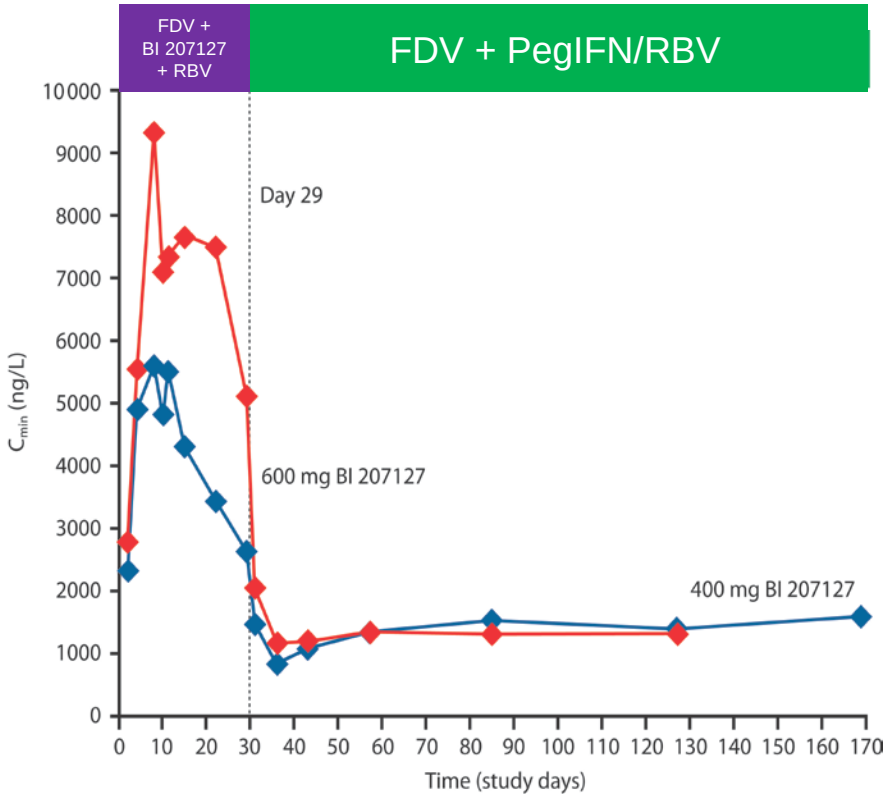
BI 207127 trough (C_{min}) concentrations



Faldaprevir trough (C_{min}) concentrations



PK data suggest that the combined administration of faldaprevir and BI 207127 transiently increases the exposure of each drug

Sabo J, et al. Hepatology 2012;56(Suppl. 1):568A

Clinical Drug-Drug Interactions with faldaprevir/BI 207127

- The combination of FDV and BI 207127 resulted in:

  Mild inhibition of CYP3A4 (midazolam AUC)
  Mild induction of CYP2C9 (tolbutamide AUC)

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