Supplemental Information

Table S1. Overview of clinical studies included in the analysis

Trial	Trial identifier(s)	Patient population	HCV GT	No. of patients	Treatment	Duration
Phase 2 studies						
SILEN-C1	NCT00774397	Treatment-naïve	GT-1	429	Placebo+PR FDV 120 mg QD + PR FDV 240 mg QD + PR +/- LI	24 weeks combination + 24 or 48 weeks PR (RGT)[a]
SILEN-C2	NCT00774397	Treatment-experienced	GT-1	288	FDV 240 mg QD + PR +/- LI FDV 240 mg BID + PR + LI	24 weeks combination + 24 or 48 weeks PR (RGT)[b]
SILEN-C3	NCT00984620	Treatment-naïve	GT-1	159	FDV 120 mg QD + PR	12 or 24 weeks combination + 24 or 48 weeks PR (RGT)
Phase 3 studies						
STARTVerso1 STARTVerso2	NCT01343888 NCT01297270	Treatment-naïve	GT-1	652 657	Placebo+PR FDV 120 mg QD + PR FDV 240 mg QD + PR	12 or 24 weeks combination[c] + 24 or 48 weeks PR (RGT)
STARTVerso3	NCT01358864	Treatment-experienced	GT-1	677	Placebo+PR FDV 240 mg QD + PR	12 or 24 weeks combination[d] + 24 or 48 weeks PR (RGT)
STARTVerso4	NCT01399619	HCV/HIV-co-infected[e]	GT-1	308	FDV 120 mg QD + PR FDV 240 mg QD + PR	12 or 24 weeks combination + 24 or 48 weeks PR (RGT)

[a]Reduced PR duration in faldaprevir 240 mg arms only.

[b]Reduced PR duration in faldaprevir 240 mg QD/LI arm only.

[c]Faldaprevir 240 mg 12 weeks, faldaprevir 120 mg 24 weeks in STARTVerso2, 12 or 24 weeks by RGT in STARTVerso1.

[d]Treatment duration by randomization.

[e]Includes treatment-naïve + treatment-experienced patients.

BID, twice daily; FDV, faldaprevir; GT, genotype; LI, 3 day PR lead-in; PR, pegylated interferon/ribavirin; QD, once daily; RGT, response-guided therapy (based on HCV RNA of <25 IU/ml at week 4 and undetectable at weeks 8 [and at week 12 for phase 2 studies]).

Table S2. GenBank Accession numbers for baseline NS3/4A sequences

Clinical Study	NS3/4A or NS3 aa1-181	Reference
1220.2 and 1220.14	KT232323 - KT232440	Berger et al. AAC 2014 (1)
SILEN-C1, C2, C3	KT232441 - KT233302	Berger et al. AAC 2014 (1) and present manuscript
STARTVerso 1,2,3,4	KT233303 - KT235564	Present manuscript

TABLE S3. Numbers of patients with NS3/4A baseline sequence data

Trial	Trial identifier(s)	Patient population	GT-1a			GT-1b		
			No. of patients in FAS	NS3 protease,[a] n (%)	NS3 helicase + NS4A,[b] n (%)	No. of patients in FAS	NS3 protease, n (%)	NS3 helicase + NS4A, n (%)
SILEN-C1	NCT00774397	Treatment-naïve + treatment-experienced	385	385 (100)	385 (100)	477	477 (100)	477 (100)
SILEN-C2	NCT00774397							
SILEN-C3	NCT00984620							
STARTVerso1	NCT01343888	Treatment-naïve	625	616 (99)	436 (70)	680	675 (99)	574 (84)
STARTVerso2	NCT01297270							
STARTVerso3	NCT01358864	Treatment-experienced	316	308 (97)	237 (75)	360	358 (99)	311 (86)
STARTVerso4	NCT01399619	HCV/HIV-co-infected[c]	242	240 (99)	145 (60)	66	65 (98)	53 (80)
		TOTAL	1568	1549 (99)	1203 (77)	1583	1575 (99)	1415 (89)

[a]NS3 amino acids 1–181.

[b]NS3 amino acids 182–631 + NS4A amino acids 1–54.

[c]Includes treatment-naïve + treatment-experienced patients.

FAS, full analysis set; GT, genotype; n, number of patients with sequence data available.

TABLE S4. Numbers of non-SVR12 patients treated with faldaprevir+PR who had post-baseline NS3/4A sequence data

Trial	Trial identifier(s)	Patient population	GT-1a			GT-1b		
			No. of patients in FAS	NS3 protease,[a] n (%)	NS3 helicase + NS4A,[b] n (%)	No. of patients in FAS	NS3 protease, n (%)	NS3 helicase + NS4A, n (%)
SILEN-C1	NCT00774397	Treatment-naïve + treatment-experienced	385	154 (40)	154 (40)	477	121 (31)	121 (31)
SILEN-C2	NCT00774397							
SILEN-C3	NCT00984620							
STARTVerso1	NCT01343888	Treatment-naïve	625	154 (25)	222 (19)	680	85 (13)	186 (17)
STARTVerso2	NCT01297270							
STARTVerso3	NCT01358864	Treatment-experienced	316	142 (45)		360	132 (37)	
STARTVerso4	NCT01399619	HCV/HIV co-infected[c]	242	57 (24)		66	11 (17)	
		TOTAL	1568	507 (32)	376 (24)	1583	349 (22)	307 (19)

Only patients with baseline and at least one post-baseline sequence are included in the table.

[a]NS3 amino acids 1–181.

[b]NS3 amino acids 182–631 + NS4A amino acids 1–54.

[c]Treatment-naïve + treatment-experienced patients.

FAS, full analysis set; GT, genotype; n, number of patients with sequence data available; PR, pegylated interferon/ribavirin; SVR12, sustained virologic response at 12 weeks post-treatment.

TABLE S5. Frequency of GT-1b NS3 helicase amino acid T344 polymorphisms in baseline samples from patients enrolled in phase 3 studies

	Frequency among baseline isolates	
Amino acid polymorphism	**TN (STARTVerso1 + 2)**	**TE (STARTVerso3)**
T344 wild-type[a]	434/574 (75.6%)	206/311 (66.2%)
T344I or I/T	87/574 (15.2%)	75/311 (24.1%)
T344V	25/574 (4.4%)	18/311 (5.8%)
T344 other[b]	28/574 (4.9%)	12/311 (3.9%)

[a]Wild-type does not include mixtures of wild-type with amino acid variants.
[b]Other variants or amino acid mixtures.
TE, treatment-experienced; TN, treatment-naïve.

TABLE S6. SVR24 rates with baseline GT-1b T344I in phase 2 studies

		With variant		Without variant		
NS3 Variant	Patient group	Total no. patients[a]	No. with SVR24 (%)	Total no. patients[b]	No. with SVR24 (%)	Fisher's P
GT-1b T344I	TN + TE pooled	93	40 (43.0)	346	263 (76.0)	**<0.0001**
	TN	52	30 (57.7)	251	217 (86.5)	**<0.0001**
	TE	41	10 (24.4)	95	46 (48.4)	**0.0131**

[a]"With variant" includes only the single amino acid variant of interest and does not include wild-type, other variants, or mixtures of the variant of interest with wild-type or other amino acids.
[b]"Without variant" includes wild-type and all other amino acid variants or mixtures detected.
GT, genotype; TE, treatment-experienced; TN, treatment-naïve; SVR24, sustained virologic response at 24 weeks post-treatment.

TABLE S7. *In vitro* characterization of NS3 S61L site-directed mutants on HCV GT-1b drug susceptibility

NS3 site-directed mutant	Mean EC_{50} nM ± SD (n)		
	FDV	SMV	TVR
Wild-type	25 ± 8 (4)	2.5 ± 0.4 (4)	930 ± 64 (4)
S61L	46 ± 25 (4)	5.7 ± 0.3 (4)	949 ± 210 (3)
D168V	29,448 ± 12,777 (4)	4281 ± 989 (4)	336 ± 46 (4)
S61L+D168V	46,447 ± 6601 (3)	3264 ± 422 (3)	425 ± 126 (3)

Means calculated from inter-experimental values.
EC_{50}, 50% effective concentration; FDV, faldaprevir; n, number of experiments; SD, standard deviation; SMV, simeprevir; TVR, telaprevir.

1. **Berger KL, Triki I, Cartier M, Marquis M, Massariol MJ, Bocher WO, Datsenko Y, Steinmann G, Scherer J, Stern JO, Kukolj G.** 2014. Baseline hepatitis C virus (HCV) NS3 polymorphisms and their impact on treatment response in clinical studies of the HCV NS3 protease inhibitor faldaprevir. Antimicrob. Agents Chemother. **58:**698-705.