High SVR rates with ABT-493 + ABT-530 co-administered for 8 weeks in non-cirrhotic patients with HCV genotype 3 infection

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BACKGROUND

- Higher rates of liver steatosis and an increased risk for hepatocellular carcinoma and fibrosis progression than other HCV genotypes[1]
- Approximately 30% of HCV infections worldwide[2]
- Now the most difficult-to-cure genotype

Figure 1. HCV Genotype 3 (GT3)

Current EASL recommendations for treatment-naïve GT3-infected patients without cirrhosis	SVR12
SOF + pegIFN/RBV for 12 weeks[3]	96%
SOF + RBV for 24 weeks[3,4]	90 – 95%
SOF + DCV for 12 weeks[5]	97%

SVR12, sustained virologic response at post-treatment week 12; SOF, sofosbuvir; pegIFN, pegylated interferon; RBV, ribavirin; DCV, daclatasvir

Figure 2. Next Generation Direct-acting Antivirals

ABT-493
Pangenotypic NS3/4A protease inhibitor

ABT-530
Pangenotypic NS5A inhibitor

***In Vitro*:[6,7]**
- High barrier to resistance
- Potent against common NS3 variants (eg., positions 80, 155 and 168) and NS5A variants (eg., positions 28, 30, 31 and 93)
- Additive/synergistic antiviral activity

Clinical PK & metabolism:
- Once-daily oral dosing
- Minimal metabolism and primary biliary excretion
- Negligible renal excretion (<1%)

ABT-493 identified by AbbVie and Enanta

Figure 3. ABT-493 and ABT-530 Have Potent Activities Against All Major HCV Genotypes, Including GT3

	Stable HCV GT3a Replicon EC_{50}		
NS3/4A Protease Inhibitor	nM	NS5A Inhibitor	pM
ABT-493	**1.6**	**ABT-530**	**2**
Grazoprevir[8]	35	Elbasvir[13]	140
GS-9857[9]	6.1	Velpatasvir[14]	20
Simeprevir[10,11]	472	Ledipasvir[15]	168,000
Paritaprevir	19	Ombitasvir	19
Asunaprevir[12]	1162	Daclatasvir[16]	530
		Odalasvir[17]	48
		MK-8408[18]	2

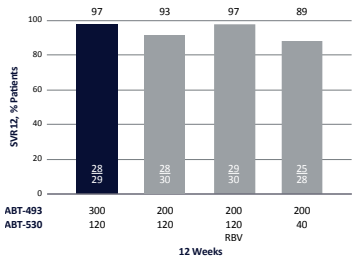
Figure 4. ABT-530 Retains Antiviral Activity Against Common GT3 Single-Position NS5A Variants

	Fold Change in EC_{50} for GT3 NS5A Variants		
NS5A Inhibitor	M28T	A30K	Y93H
ABT-530	**0.4**	**1.1**	**2.5**
Ledipasvir[19]	N/A	>1000	>1000
Velpatasvir[20]	N/A	10 – 100	>100
Daclatasvir[21]	46	56 – 62	2738 – 2752
Elbasvir[22]	N/A	50	486
Ombitasvir[23]	423	N/A	6728
Odalasvir	N/A	N/A	N/A
MK-8408	N/A	N/A	N/A

N/A, not available

PRIOR RESULTS IN PATIENTS WITH GT3 INFECTION, AND OBJECTIVE

- Dose-ranging part 1 of this study with ABT-493 300 mg + ABT-530 120 mg resulted in 97% (28/29) mITT SVR12 in treatment-naïve or -experienced patients without cirrhosis treated for 12 weeks[24]



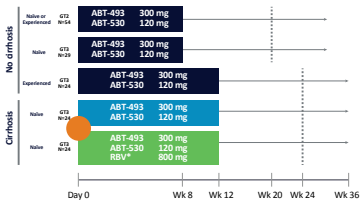
OBJECTIVE

- Explore whether a shorter 8-week treatment duration with ABT-493 + ABT-530 would result in a similarly high SVR rate in treatment-naïve GT3-infected patients without cirrhosis

RESULTS

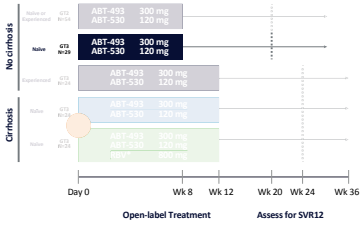
Figure 5A. SURVEYOR-II Part 2 Study Design

- Partially randomised, open-label, multicentre phase 2 trial evaluating the dose combination of ABT-493 300 mg and ABT-530 120 mg identified in the dose-ranging part 1 of this study



*RBV dosed once-daily.
Orange circle = randomised arms.

Figure 5B. SURVEYOR-II Part 2 Study Design



*RBV dosed once-daily.
Orange circle = randomised arms.

PATIENT INCLUSION CRITERIA

- 18 to 70 years of age, inclusive
- HCV GT3 infection, HCV RNA >10,000 IU/mL
- Absence of cirrhosis

PATIENT EXCLUSION CRITERIA

- Any prior HCV treatment
- HIV co-infection
- Herbal supplements and potent P-gp inducers were prohibited

ENDPOINTS

- Efficacy: SVR12 (primary) and virologic failure
- Safety: adverse events (AEs) and laboratory abnormalities

Figure 6. Demographics and Patient Characteristics

	ABT-493 + ABT-530 (N = 29)
Male, n (%)	15 (52)
Race, n (%)	
White	26 (90)
Black	1 (3)
Hispanic/Latino, n (%)	2 (7)
Age, mean years (range)	47 (27 – 66)
BMI, mean kg/m^2, ± SD	26 ± 3.8
HCV RNA, median $\log_{10}$ IU/mL (range)	6.5 (5.0 – 7.5)
CV GT3a*, n (%)	25 (86)
Baseline fibrosis stage, n (%)	
F0 – F1	20 (69)
F2	2 (7)
F3	7 (24)

* Genotypes were determined using the Versant HCV Genotype Inno-LIPA Assay, version 2.0 or higher Subgenotype (per the central lab) was not determined for 3 patients.

Figure 7. Baseline Variants in NS3 and NS5A

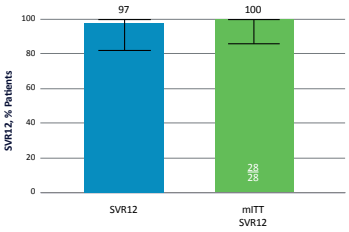
	ABT-493 + ABT-530 (N = 28*)
Any variants, n (%)	13 (46)
NS5A only, n	10
NS3 only, n	2
Both NS3 and NS5A variants, n	1

* Sequencing pending for 1 patient. Variants detected by population sequencing (detection threshold of 15%).

NS3 variants:	NS5A variants:
A166S (n = 3)	Y93H (n = 5)
	A30K/S/V (n = 5)
	P58A/T (n = 2)

- Variants detected by population sequencing (detection threshold of 15%) at the following amino acid positions that confer resistance to at least 1 DAA in the inhibitor class were included in the analysis; they may not confer resistance to ABT-493 or ABT-530.
- NS3: 36, 56, 80, 155, 156, 166, and 168
- NS5A: 24, 28, 29, 30, 31, 32, 58, 92, and 93

Figure 8. SVR12 Analysis



mITT SVR12 rate excludes non-virologic failures

- No virologic failures
- 1 patient withdrew consent after treatment week 6 due to intolerance of blood draws and had an undetectable HCV RNA at the time of discontinuation

Figure 9. Summary of Adverse Events

Event, n (%)	ABT-493 + ABT-530 (N = 29)
Any AE	22 (76)
AE leading to study drug discontinuation	0
Serious AE	0
Common AEs*	
Headache	5 (17)
Fatigue	3 (10)
Diarrhoea	3 (10)
Insomnia	3 (10)
Oropharyngeal pain	3 (10)
Toothache	3 (10)

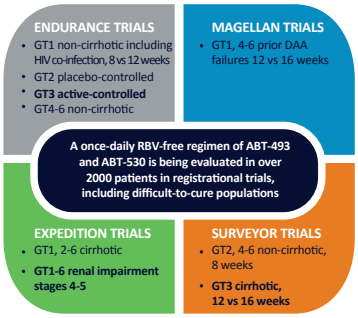
Figure 10. Laboratory Abnormalities

Event, n	ABT-493 + ABT-530 (N = 29)
ALT, grade ≥2 (>3 x ULN)*	0
AST, grade ≥2 (>3 x ULN)*	0
Total bilirubin	
Grade 2 (>1.5 – 3 x ULN)	1
Grade ≥3 (>3 x ULN)	0
Alk phos, grade ≥2 (>2.5 x ULN)	0
Haemoglobin, grade ≥2 (<10 g/dL)	0

* Post nadir

- In all patients with baseline ALT elevations, ALT levels normalised with treatment and no on-treatment ALT elevations were observed
- No grade 3 or 4 abnormalities were observed

Figure 11. Based on These Data, ABT-493 and ABT-530 are Being Evaluated as a Pangenotypic RBV-free Regimen



CONCLUSIONS

- 8-week treatment with once-daily ABT-493 and ABT-530 achieved 97% SVR12 in treatment-naïve GT3-infected patients without cirrhosis
- There were no virologic failures; 100% mITT SVR12
- High efficacy was achieved regardless of baseline viral load or presence of baseline NS3 and/or NS5A variants
- This combination was well tolerated, with mostly mild AEs, no serious AEs, no significant laboratory abnormalities, and no discontinuations due to AEs.

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This presentation contains information on the investigational products ABT-493 and ABT-530.

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