SUPPLEMENTAL DIGITAL CONTENT LEGENDS

Eligibility Criteria, Supplement 1

B. EXCLUSION CRITERIA

1. Female subject who is pregnant, breastfeeding, or is considering becoming pregnant during the study or for approximately 30 days after stopping study drug (if not receiving RBV), or for up to 4 months after stopping study drug if receiving RBV (or as directed by local RBV label).
2. Use of known strong inducers and inhibitors (eg, gemfibrozil) of cytochrome P450 2C8 (CYP2C8) in patients receiving dasabuvir, or strong or moderate inducers of CYP3A, medications listed below, or medications contraindicated for ritonavir or RBV (for those who receive RBV), within 2 weeks or 10 half-lives, whichever is longer, of the respective medication prior to administration of study drugs, including but not limited to:

Table. Medications contraindicated for use with the study drug regimen

For medications contraindicated with AbbVie's ombitasvir/paritaprevir/ritonavir with dasabuvir, refer to the recommended prescribing information section of the approved local product labels in countries where the regimen contained in this study (ie, ombitasvir/paritaprevir/ritonavir with dasabuvir) has received marketing authorization. If locally approved labels are not available, refer to the following Contraindicated Medication list:

Alfuzosin	Ergotamine	Phenytoin
Astemizole	Ergonovine	Pimozide
Atorvastatin	Ethinyl estradiol-containing medications	Ranolazine
Blonanserin	Fusidic acid	Rifampin
Carbamazepine	Gemfibrozil‡	Salmeterol
Cisapride	Lovastatin	Sildenafil†
Colchicine*	Lurasidone	Simvastatin
Dihydroergotamine	Methylergonovine	St. John's wort
Dronedarone	Midazolam (oral)	Terfenadine
Efavirenz	Phenobarbital	Triazolam

*When used in patients with renal or hepatic impairment.
†When used for the treatment of pulmonary arterial hypertension.
‡Strong CYP2C8 inhibitors (e.g., gemfibrozil) and CYP2C8 inducers are not contraindicated with ombitasvir, paritaprevir and ritonavir (for GT4 patients).
Note: Not all medications contraindicated with RBV are listed above. Refer to the most current package inserts or product labeling of RBV for a complete list of contraindicated medications.

3. Clinically significant abnormalities or comorbidities, other than HCV infection that make the subject an unsuitable candidate for this study or treatment with RBV (if applicable) in the opinion of the investigator.
4. Positive test result for hepatitis B virus surface antigen or anti-HIV antibody test.

5. Current enrollment in another interventional clinical study, previous enrollment in this study, prior or current use of any investigational or commercially available anti-HCV agents other than IFNs or RBV, or receipt of any investigational product within 6 weeks prior to study drug administration.
6. History of solid organ transplant.
7. Prior or current use of any investigational or commercially available anti-HCV agents other than IFN, pegIFN or RBV, including telaprevir, boceprevir, sofosbuvir, ombitasvir, dasabuvir, paritaprevir, ledipasvir, daclatasvir, simeprevir, elbasvir, grazoprevir, or an investigational direct-acting antiviral.
8. Screening laboratory analyses showing any of the following abnormal laboratory results:

- Albumin <2.8 g/dL
- Hemoglobin <10 g/dL
- Platelets <25,000 cells/mm^3
- Total bilirubin >3.0 mg/dL

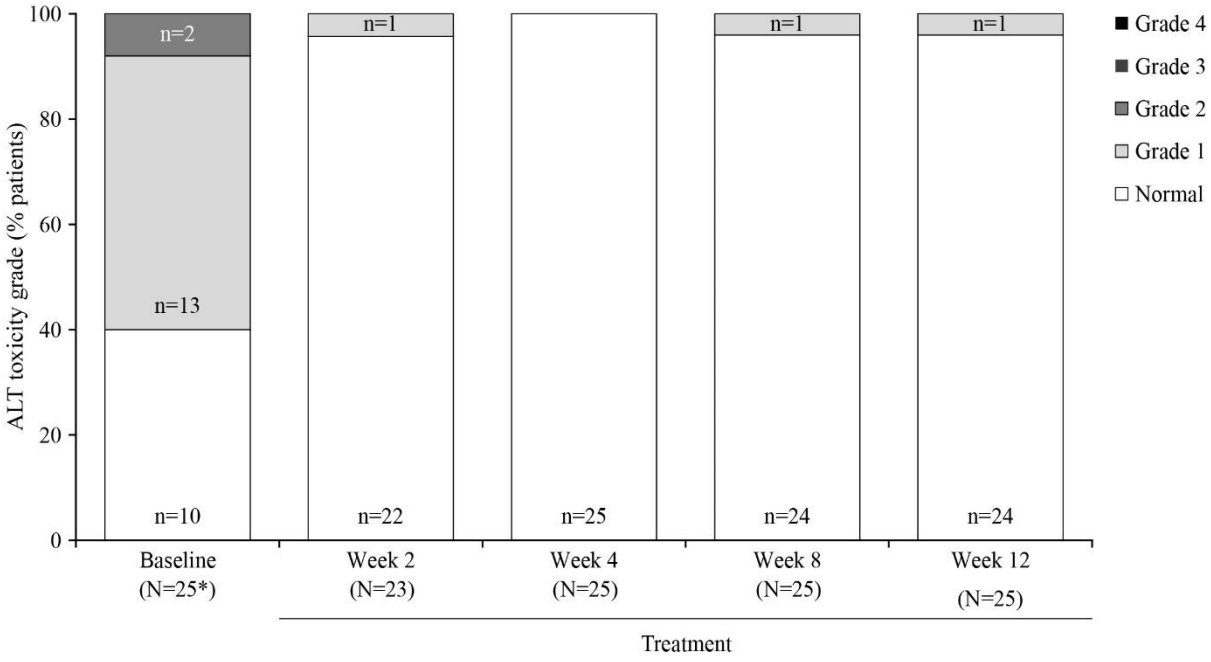
9. Any current or past clinical evidence of Child-Pugh B or C classification (Child-Pugh score ≥7), or clinical history of liver decompensation such as ascites (noted on physical examination), variceal bleeding, or hepatic encephalopathy.
10. Confirmed presence of hepatocellular carcinoma indicated on imaging techniques such as computed tomography (CT) scan or magnetic resonance imaging (MRI) within 3 months prior to screening or on an ultrasound performed at screening for patients with cirrhosis (a positive ultrasound result will be confirmed with CT scan or MRI).
11. Male subject who is considering fathering a child or donating sperm during the study or for approximately 120 days after stopping study drug if receiving DAAs only, or for up to 7 months after stopping study drug if receiving RBV (or as directed by local RBV label).

Supplemental 2: Pharmacokinetic Assessments

Blood samples were collected for intensive pharmacokinetic analysis at 2, 4, 8, 12, and 24 hours post dose at the Week 2 visit. Additional sparse samples were taken on Day 1 (at 4 hours post dose), Week 4 (regardless of dosing time), Week 8 (trough sample), and Week 12 (regardless of dosing time). Plasma concentrations of study drugs and DSV M1 metabolite were determined using validated analytical methods developed by the Drug Analysis Department at AbbVie. The primary pharmacokinetic endpoints were the maximum plasma concentrations (C_{max}) and the area under the plasma concentration–time curve (AUC) (at 0 to 24 hours for OBV, PTV, and ritonavir, or 0 to 12 hours for DSV and DSV M1) following dosing at Week 2 and trough concentrations (C_{trough}) following dosing at Weeks 2 and 8.

Figure, Supplement 3
Percentage of patients with ALT Grades normal, 1, 2, 3, or 4 by treatment visit (safety population; observed cases). Clinical severity CTCAE Grade 1, ≥3 × ULN; Grade 2, >3–5 × ULN; Grade 3, >5–30 × ULN; Grade 4, >20 × ULN. *Excluded 1 patient who discontinued from study treatment 9 days after treatment initiation.

ALT = alanine aminotransferase; CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ULN = upper limit of normal.



Supplement 4. Summary statistics of pharmacokinetic parameters by weight group

		C_{max} (ng/mL)	T_{max}[a] (h)	AUC[b] (ng•h/mL)	Week 2 C_{trough} (ng/mL)	Week 8 C_{trough} (ng/mL)
Ombitasvir						
15–29	12	99.6 (27)	4.0	1270 (26)	24.7 (32)	29.6 (78)[c]
		63.9–154	4.0–4.5	776–1850	11.7–37.5	8.06–90.7
30–44	9	116 (14)	4.0	1490 (12)[d]	28.2 (16)[d]	30.4 (24)[e]
		97.3–148	4.0–4.0	1260–1790	22.9–34.3	21.4–40.9
≥45	13	83.7 (39)	4.0	1060 (43)[f]	21.8 (39)[f]	20.9 (58)[c]
		46.1–150	2.0–8.0	664–2210	14.5–42.3	0–44.5
Paritaprevir						
15–29	12	294 (152)	4.0	2180 (136)	9.86 (113)	17.3 (136)
		47.4–3610	2.0–4.5	447–19100	2.89–63.9	1.00–83.9
30–44	9	1540 (71)	4.0	8640 (90)[d]	16.1 (112)[d]	18.4 (89)[e]
		272–4190	2.0–4.0	1640–34900	3.15–96.9	4.16–50.8
≥45	13	870 (125)	4.0	5770 (152)[f]	18.0 (78)[f]	23.5 (86)[c]
		266–6590	4.0–8.0	2020–55500	5.86–63.9	0–69.2
Ritonavir						
15–29	12	1090 (67)	2.0	6570 (60)	16.1 (72)	91.8 (268)
		199–3050	2.0–4.0	1520–16200	8.57–54.6	0–855
30–44	9	1830 (42)	2.4	14100 (49)	32.1 (63)	38.1 (112)[e]
		851–3230	2.0–4.0	6760–29700	8.14–89.3	12.1–133
≥45	13	1180 (35)	4.0	8900 (37)[f]	29.8 (54)[f]	58.2 (138)[c]
		397–1940	2.0–8.0	3640–17800	12.2–81.2	0–278

Dasabuvir						
15–29	12	579 (44)	4.0	3960 (44)[g]	110 (57)	168 (82)
		292–1180	2.0–8.0	1820–8630	54.9–281	12.3–426
30–44	9	830 (45)	4.0	5960 (47)[g]	215 (54)	264 (65)[e]
		549–1840	2.0–4.0	4230–13700	117–518	120–621
≥45	13	671 (48)	4.0	4630 (49)	165 (56)	191 (60)[c]
		241–1470	2.0–8.0	1820–10200	42.0–469	11.4–361
Dasabuvir M1 metabolite						
15–29	12	173 (75)	4.0	1140 (72)[g]	25.4 (77)	45.5 (135)
		89.7–563	2.0–8.0	689–3900	11.0–97.6	0–231
30–44	9	336 (34)	4.0	2320 (38)[g]	64.8 (53)	65.2 (44)[e]
		181–525	4.0–4.0	1130–3740	23.5–131	41.8–116
≥45	13	312 (43)	4.0	2010 (44)	55.9 (58)	54.7 (57)[c]
		72.8–680	2.0–8.0	649–4020	26.4–48	0–89.6
Ribavirin						
15–29	12	2100 (28)	2.0	19000 (24)[g]	1300 (25)	1720 (40)[cd]
		1060–2790	2.0–4.0	11200–25300	759–1930	469–2560
30–44	9	2440 (16)	2.0	24200 (15)[g]	1710 (15)	2170 (16)[e]
		1940–3030	2.0–4.0	19500–29600	1320–2130	1720–2910
≥45	9	2320 (26)	2.0	22800 (24)	1590 (23)	2080 (45)[e]
		1300–2970	2.0–4.0	13800–29900	998–2120	778–3090

Data are geometric mean (%CV) and range unless stated otherwise.

$AUC_{0–12}$ = area under the plasma concentration–time curve from time 0 to 12 hours; $AUC_{0–24}$ = area under the plasma concentration–time curve from time 0 to 24 hours; CV = coefficient of variation; T_{max} = time to maximum observed plasma concentration.

[a] Median and range.

[b] $AUC_{0–24}$ for ombitasvir, paritaprevir, and ritonavir; $AUC_{0–12}$ for dasabuvir, dasabuvir M1, and ribavirin.

[c] N = 11.

[d] N = 8.

[e] N = 7.

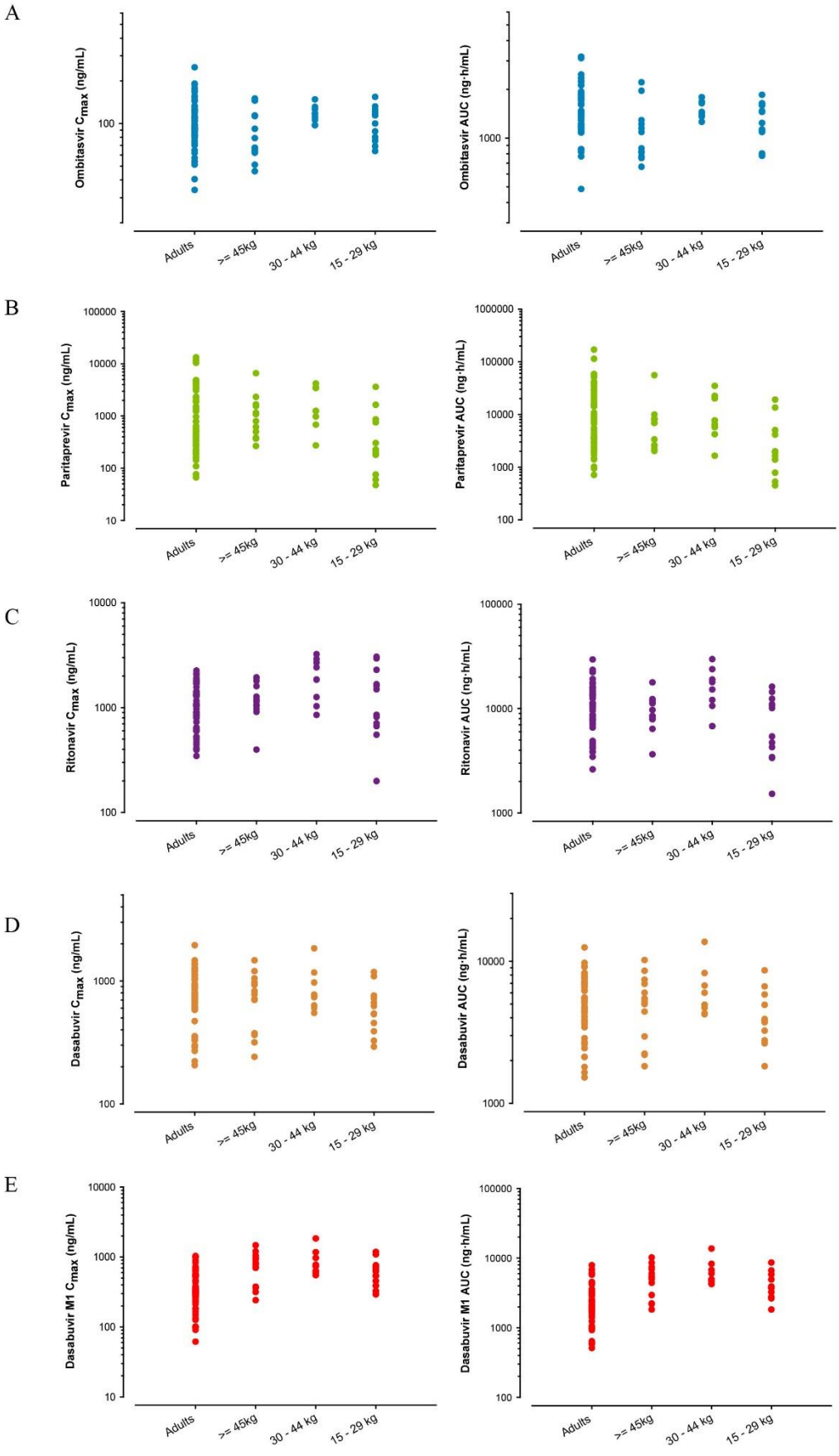
[f] N = 12.

[g] For 2 patients, the 24-hour concentration was used as the 12-hour concentration because of significant sampling time deviation

Figure, Supplement 5

Comparison of individual C_{max} and AUC values between historical data in adults and pediatric weight groups. **A–C.** $AUC_{0–24}$ for OBV, PTV, ritonavir, and DSV. **D.** $AUC_{0–12}$ for DSV. **E.** $AUC_{0–12}$ for DSV M1 metabolite. The pediatric patients in the ≥45-kg group were adolescents using adult tablet formulation and children aged 9–11 years using pediatric mini-tablet formulations. Patients in the 30–44-kg and 15–29-kg groups were aged 3–11 years using pediatric mini-tablet formulations.

$AUC_{0–12}$ = area under the plasma concentration–time curve from time 0 to 12 hours; $AUC_{0–24}$ = area under the plasma concentration–time curve from time 0 to 24 hours; C_{max} = maximum plasma concentrations; DSV = dasabuvir; OBV = ombitasvir; PTV = paritaprevir.


A
Ombitasvir C_{max} (ng/mL)
100
Ombitasvir AUC (ng·h/mL)
1000
B
Paritaprevir C_{max} (ng/mL)
100000
10000
1000
100
10
Paritaprevir AUC (ng·h/mL)
1000000
100000
10000
1000
100
C
Ritonavir C_{max} (ng/mL)
10000
1000
100
Ritonavir AUC (ng·h/mL)
100000
10000
1000
D
Dasabuvir C_{max} (ng/mL)
1000
100
Dasabuvir AUC (ng·h/mL)
10000
1000
E
Dasabuvir M1 C_{max} (ng/mL)
10000
1000
100
10
Dasabuvir M1 AUC (ng·h/mL)
100000
10000
1000
100
Adults
>= 45kg
30 - 44 kg
15 - 29 kg