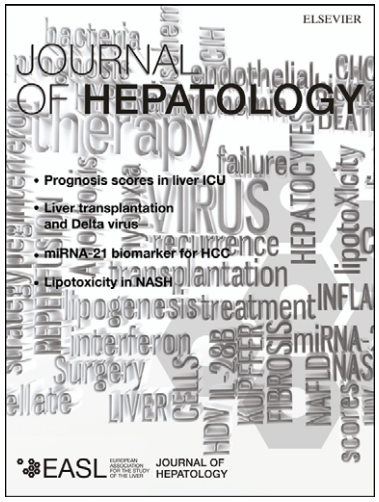

Dual Oral Therapy with Daclatasvir and Asunaprevir for Patients with HCV Genotype 1b Infection and Limited Treatment Options

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Abbreviations:

HCV	hepatitis C virus
DAA	direct-acting antiviral
Alfa/RBV	peginterferon alfa and ribavirin
SVR	sustained virologic response
HIV	human immunodeficiency virus
NS5A	nonstructural protein 5A
NS3	nonstructural protein 3
ALT	alanine aminotransferase
ULN	upper limit of the normal reference range
INR	international normalized ratio
CYP3A4	cytochrome P450 3A4

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ABSTRACT

Background & Aims

Improved therapeutic options for chronic hepatitis C virus (HCV) infection are needed for patients who are poor candidates for treatment with current regimens due to anticipated intolerability or low likelihood of response.

Methods

In this open-label, phase 2a study of Japanese patients with chronic HCV genotype 1b infection, 21 null responders (<2 $\log_{10}$ HCV RNA reduction after 12 weeks of peginterferon/ribavirin) and 22 patients intolerant to or medically ineligible for peginterferon/ribavirin therapy received dual oral treatment for 24 weeks with the NS5A replication complex inhibitor daclatasvir (DCV) and the NS3 protease inhibitor asunaprevir (ASV). The primary efficacy endpoint was sustained virologic response at 12 weeks posttreatment (SVR_{12}).

Results

Thirty-six of 43 enrolled patients completed 24 weeks of therapy. Serum HCV RNA levels declined rapidly, becoming undetectable in all patients on therapy by week 8. Overall, 76.7% of patients achieved SVR_{12} and SVR_{24}, including 90.5% of null responders and 63.6% of ineligible/intolerant patients. There were no virologic failures among null responders. Three ineligible/intolerant patients experienced viral breakthrough and four relapsed posttreatment. Diarrhea, nasopharyngitis, headache, and ALT/AST increases, generally mild, were the most common adverse events; three discontinuations before week 24 were due to adverse events that included hyperbilirubinemia and transaminase elevations (two patients).

Conclusions: Dual therapy with daclatasvir and asunaprevir, without peginterferon/ribavirin, was well tolerated and achieved high SVR rates in two groups of difficult-to-treat patients with hepatitis C virus genotype 1b infection.

INTRODUCTION

Therapies for chronic hepatitis C virus (HCV) infection have improved markedly over the past decade. The recent approval of the first direct-acting antivirals (DAAs) was an important milestone in the evolution of HCV therapy, establishing that DAAs can enhance regimen efficacy and provide durable viral clearance. These new agents in combination with peginterferon and ribavirin (alfa/RBV) achieve overall sustained virologic response (SVR) rates of approximately 70% in treatment-naïve patients with HCV genotype 1 infection.[1, 2]

Despite these advances, current treatment options remain inadequate for some patients. Patients with prior null response to alfa/RBV (<2 $\log_{10}$ decline in HCV RNA after 12 weeks) have a particularly acute need for further therapeutic improvements. Null responders generally respond poorly to retreatment with alfa/RBV; fewer than 10% achieve SVR.[3] Retreatment of null responders with alfa/RBV combined with telaprevir or boceprevir increases SVR rates to approximately 30%–38%, suggesting that addition of a DAA to alfa/RBV increases efficacy but that more potent regimens are still urgently needed.[4, 5] There are also many patients who cannot be treated with current therapies; this group includes patients with prior intolerance to alfa/RBV and patients who are ineligible for alfa/RBV-containing therapy for medical reasons.

There is precedence for use of combination antiviral regimens to treat human immunodeficiency virus (HIV) infections; evidence is mounting that DAA regimens can also provide durable clearance

of HCV infections. Thus, there is a strong rationale for exploration of dual DAA regimens, without alfa/RBV. In combination, DAAs with different molecular targets can increase regimen potency and raise the barrier to resistance, potentially eliminating the need for alfa/RBV and providing a viable therapy for patients who are anticipated to be poorly responsive or intolerant to current alfa/RBV-containing regimens. The improved tolerability and convenience that can be anticipated with dual DAA regimens suggests that they may also benefit treatment-naïve patients and other groups. Previous studies of DAA-only regimens, or DAAs combined with RBV, have demonstrated marked antiviral effects in treatment-naïve and experienced patients, including null responders, supporting the further evaluation of dual DAA therapy reported here.[6-10]

Daclatasvir (DCV; BMS-790052) is a first-in-class, highly selective NS5A replication complex inhibitor with picomolar potency and broad genotypic coverage; asunaprevir (ASV; BMS-650032) is a potent NS3 protease inhibitor active against genotypes 1 and 4. Daclatasvir and asunaprevir have different modes of action and resistance-associated variants, and in combination show increased antiviral potency *in vitro* and a high genetic barrier to resistance.[11, 12] Daclatasvir and asunaprevir had no clinically meaningful pharmacokinetic interaction in healthy volunteers.[13] Initial efficacy evaluations of daclatasvir and asunaprevir (DUAL therapy) showed potent antiviral effects and SVR rates ≥90% in Japanese and US/European null responders with HCV genotype 1b infection.[7, 8]

We present final results of an open-label trial evaluating DUAL oral therapy with daclatasvir and asunaprevir in Japanese patients with chronic HCV genotype 1b infection. Initial results from a sentinel cohort of 10 patients with prior null response to alfa/RBV have been reported.[7] The present report combines these data with results for 11 additional null responders, together with

results for 22 patients with prior intolerance to alfa/RBV or who were medically ineligible for alfa/RBV-containing therapy.

METHODS

Study design

This open label, phase 2a study (AI447-017; clinicaltrials.gov identifier NCT01051414) was conducted in two populations of patients with HCV genotype 1 infection, including null responders (<2 $\log_{10}$ decline of serum HCV RNA levels after 12 weeks of prior alfa/RBV), and alfa/RBV ineligible/intolerant patients. The latter group discontinued prior therapy with alfa/RBV due to intolerance after <12 weeks, or were treatment-naïve but poor candidates for alfa/RBV for medical reasons such as advanced age or complications of depression, anemia, myelosuppression, diabetes, or cardiovascular or renal dysfunction.

Patients were enrolled in two cohorts of null responders and two cohorts of alfa/RBV ineligible/intolerant patients. One cohort of each population included intensive sampling for pharmacokinetic analyses; both cohorts of each population were combined for efficacy and safety assessments. The sentinel cohort of null responders, reported previously, provided 4-week safety data for review by the study Safety Committee prior to initiation of the other cohorts.[7] The primary efficacy endpoint was the proportion of patients with undetectable HCV RNA at 12 weeks posttreatment (SVR_{12}). Key secondary endpoints included the proportions of patients with HCV RNA undetectable at week 4, week 12, the end of treatment, and posttreatment week 24 (SVR_{24}).

Written informed consent was obtained from all patients. The study was approved by institutional review boards at each site and was conducted in compliance with the Declaration of Helsinki, Good Clinical Practice Guidelines, and local regulatory requirements.

Patients

Eligible patients were men and women aged 20–75 years with HCV genotype 1 infection ≥6 months and HCV RNA ≥10^5 IU/mL. Women of childbearing potential were using adequate contraception. Patients were excluded if they had evidence of liver cirrhosis within 24 months of screening by laparoscopy, imaging studies, or liver biopsy; a history of hepatocellular carcinoma, other chronic liver disease, variceal bleeding, hepatic encephalopathy, or ascites requiring diuretics or paracentesis; coinfection with hepatitis B virus or HIV; other clinically significant medical conditions; exposure to any investigational drug or placebo within 4 weeks, or any previous exposure to NS5A or NS3 protease inhibitors.

Exclusionary laboratory findings included alanine aminotransferase (ALT) >5 x upper limit of normal (ULN), total bilirubin ≥2 mg/dL, direct bilirubin >1.5 xULN, international normalized ratio (INR) ≥1.7, albumin ≤3.5 g/dL, hemoglobin <9.0 g/dL, white blood cells <1,500/mm^3, absolute neutrophils <750 /mm^3, platelets <50,000/mm^3, and creatinine >1.8 xULN. Prohibited concomitant medications included CYP3A4 inducers or moderate/strong CYP3A4 inhibitors, non-study medications with anti-HCV activity, prescription or herbal products not prescribed for treatment of a specific condition, proton pump inhibitors, and erythropoiesis-stimulating agents. Prescribed H2 receptor antagonists were administered ≥2 hours after and ≥10 hours prior to daclatasvir; other acid modifying agents were administered ≥2 hours prior and ≥2 hours after daclatasvir.

Study drug dosing

Patients received 24 weeks of treatment with daclatasvir 60 mg once daily (two 30 mg tablets) combined with asunaprevir 200 mg twice daily, with 24 weeks of posttreatment follow-up. In the sentinel cohort of null responders, asunaprevir was initially administered as three 200 mg tablets twice daily (600 mg BID), subsequently reduced to 200 mg BID during treatment following reports from another study of greater and more frequent aminotransferase elevations with the higher dose.[14]

Patients with HCV RNA <15 IU/mL on or after week 4 continued treatment to week 24; patients discontinued treatment if HCV RNA decreased <2 $\log_{10}$ IU/mL from baseline, on or after week 2. Patients with viral breakthrough on or after week 2, or quantifiable HCV RNA (≥15 IU/mL) on or after week 4, either discontinued treatment or weight-based alfa/RBV was added (null responders only) for up to 48 additional weeks at the discretion of the investigator based on anticipated tolerability. Viral breakthrough was defined as confirmed ≥1 $\log_{10}$ IU/mL increase from nadir of HCV RNA, or HCV RNA ≥15 IU/mL after confirmed undetectable. Posttreatment relapse was defined as confirmed HCV RNA ≥15 IU/mL during follow-up in patients with undetectable HCV RNA at the end of treatment.

Safety and efficacy assessments

HCV RNA, physical examinations, adverse events, laboratory parameters, and concomitant medications were assessed at screening, study days 1 (baseline), weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24, and posttreatment weeks 4, 8, 12, and 24. Twelve-lead electrocardiograms were recorded at all visits except weeks 3 and 6.

Serum HCV RNA levels were determined at a central laboratory using the Roche COBAS® TaqMan® HCV Auto assay, (Roche Diagnostics KK, Tokyo, Japan), lower limit of quantitation 15 IU/mL. HCV genotype and subtype and *IL28B* genotype (rs12979860) were determined by PCR amplification and sequencing. Baseline liver fibrosis was assessed by serum blood markers (APRI; AST and Platelet Ratio Index).[15] HCV resistance-associated polymorphisms were analyzed in stored baseline samples from all patients and post-failure samples from patients with viral breakthrough or posttreatment relapse. Polymorphisms were analyzed by PCR amplification and population sequencing of the HCV NS3 protease and NS5A domains.

Statistical analysis

Categorical variables were summarized using counts and percents; continuous variables were summarized with univariate statistics.

RESULTS

Patient characteristics and disposition

Forty-nine patients were screened of which six failed to meet entry criteria; 21 null responders and 22 ineligible/intolerant patients were enrolled and treated (Table 1). The enrolled population was generally older (median 62 years), consistent with HCV epidemiology in Japan, and primarily female (67%); all patients were Japanese. No patient had prior exposure to HCV DAAs. Although any HCV genotype 1 subtype was permitted, all enrolled patients had genotype 1b infection, reflecting the high proportion of this subtype in Japan.[16] Null responders were primarily IL28B genotype CT (rs12979860) as expected [17]; Ineligible/intolerant patients were primarily genotype

CC, consistent with the distribution of IL28B genotypes in Japan.[18] Eighteen ineligible/intolerant patients were treatment-naïve and considered ineligible for alfa/RBV due to anticipated difficulty in completing therapy due to advanced age (≥70 years); seven patients), cytopenia (two), depression (two), hypertension (one), or other reasons (six), consistent with common clinical practice in Japan. Four patients had prior alfa/RBV intolerance due to cytopenia (two patients), depression (one), or other reasons (one). Baseline HCV RNA and ALT levels were similar across patient groups. Although patients with cirrhosis by imaging criteria were excluded, four enrolled patients had APRI scores >2 at baseline, indicating probable cirrhosis.[15]

Thirty-six of 43 enrolled patients completed 24 weeks of therapy (Fig. 1). Two null responders discontinued study medication due to hyperbilirubinemia (week 2) and aminotransferase elevation (week 12), respectively. One null responder achieved very low HCV RNA (50 IU/mL) at Week 4; however, stringent protocol-defined rules required discontinuation from DAA-only therapy and addition of alfa/RBV to the dual DAA regimen at Week 6. Study drugs were discontinued in four ineligible/intolerant patients due to aminotransferase elevation (week 16), viral breakthrough (week 16), or patient request (weeks 8 and 16); all four remained on study for assessment of SVR.

Virologic response

High rates of virologic response were seen at all timepoints in both study populations (Table 2). Overall, 77% of patients achieved SVR_{12} and SVR_{24}. HCV RNA was undetectable in more ineligible/intolerant patients than null responders at week 4, suggesting a more rapid initial antiviral effect, but HCV RNA was undetectable in similar proportions of both populations at week

12 and the end of treatment. Rates of SVR_{24} were higher in null responders (91%) than in ineligible/intolerant patients (64%) due to virologic failures in the latter group (3 breakthroughs and 4 relapses). Assessment of virologic response by IL28B genotype (rs12979860) showed slightly greater responses at weeks 2, 3, and 4 in patients with genotype CC; however, similar proportions of patients with genotypes CC and CT achieved SVR_{24} (Fig. 2). All four patients with possible cirrhosis based on APRI score achieved SVR_{24}.

HCV RNA declined rapidly after initiation of therapy in all patients (Fig. 3). Mean reductions of HCV RNA from baseline at week 4 were 5.6 and 5.4 $\log_{10}$ IU/mL in null responders and ineligible/intolerant patients, respectively; HCV RNA was undetectable by week 8 in all patients on therapy. In the ineligible/intolerant group, initial virologic response in the four intolerant patients was similar to that of the cohort overall; three of these patients subsequently achieved SVR_{24} and one relapsed. The null responder who discontinued at week 2 with hyperbilirubinemia had low-level HCV RNA at discontinuation and undetectable HCV RNA at all posttreatment assessments. The null responder who added alfa/RBV at week 6 received 46 weeks of quadruple therapy and HCV RNA remained undetectable 24 weeks posttreatment. Among the four ineligible/intolerant patients who discontinued study drugs before week 24, HCV RNA was undetectable at discontinuation (weeks 8 or 16) in three patients and remained undetectable in the two patients who completed posttreatment follow-up.

Viral breakthrough and relapse

No null responders experienced virologic breakthrough or relapse (Table 2). Three ineligible/intolerant patients experienced viral breakthrough at weeks 10 or 16 after ≥4 weeks with undetectable serum HCV RNA, and four patients relapsed at posttreatment week 4 (three

patients) or 12 (one patient) after ≥18 weeks with undetectable HCV RNA. All three patients with viral breakthrough were IL28B genotype CT (rs12979860), compared with 6/22 ineligible/intolerant patients overall. Three patients who relapsed were IL28B genotype CC; one was genotype CT.

Resistance-associated polymorphisms in NS5A and/or NS3 protease were found pretreatment in 33/43 patients overall, most of whom achieved SVR. Daclatasvir and asunaprevir resistance-associated variants were detected post-failure in all seven patients with virologic failure (Table 3). The NS5A-Y93H variant pre-existed in 10/43 study patients, of which five (50%) experienced virologic failure and five (50%) achieved SVR. NS5A-L31 and NS3-D168 substitutions emerged in all failures, but were not detected pretreatment except for NS5A-L31M in one patient.

In general, patients with virologic failure had concurrent asunaprevir and daclatasvir trough concentrations below median values, but within the expected range (Fig. 4). Notably, most patients with trough concentrations below median values achieved SVR. There were no strong associations between virologic failure and pretreatment parameters that included gender, age, baseline HCV RNA level, IL28B genotype, reason for alfa/RBV ineligibility, and fibrosis stage. Adherence to treatment, assessed by pill counts at study visits, was high in six of the seven patients with virologic failure.

Safety

The most frequently reported adverse events were generally mild headache, nasopharyngitis, aminotransferase elevations, and diarrhea (Table 4). The most frequent grade 3 or 4 laboratory abnormalities were serum aminotransferase elevations. There were six serious adverse events in

five patients, including grade 2/3 pyrexia (three patients), grade 2 exacerbation of hypochondriasis, and grade 2 gastroenteritis (unrelated to study drugs) with grade 4 hyperbilirubinemia (described in detail previously).[7] All three pyrexia events resolved after 4–10 days with continued study treatment; the hypochondriasis persisted for approximately six months and resolved after completion of study treatment. In the patient who discontinued with hyperbilirubinemia, bilirubin normalized four weeks posttreatment.[7] Serum aminotransferases normalized by four weeks posttreatment in the two patients who discontinued for elevations.

DISCUSSION

High rates of SVR_{24} were achieved after 24 weeks of dual oral DAA therapy in null responders and alfa/RBV ineligible or intolerant patients, representing two populations that are particularly difficult to treat due to limited therapeutic options. SVR rates were comparable at posttreatment weeks 4, 12 and 24; only one relapse occurred more than 4 weeks posttreatment. The 90.5% SVR rate in null responders is substantially higher than the generally poor response to alfa/RBV retreatment and the 37% SVR rate reported for genotype 1b null responders treated with alfa/RBV and telaprevir.[4, 19] Therefore, therapy of this population with daclatasvir and asunaprevir appeared to overcome their poor interferon responsiveness, which may be less relevant to the efficacy of this DAA-only regimen. The SVR rate of 63.6% in ineligible/intolerant patients, although lower than results in null responders, is the first demonstration of a potentially effective treatment for these patients who currently have no therapeutic options. High SVR rates in both populations were achieved despite multiple adverse predictors of response to alfa/RBV therapy,

including older age, high viral load, and a high proportion of IL28B genotype CT in the null responders.

Detectable HCV RNA was cleared rapidly; viral suppression was greater at all timepoints than reported results with alfa/RBV combined with telaprevir or TMC435 in genotype 1 null responders.[4, 20] The slightly greater early viral suppression in ineligible/intolerant patients may reflect the higher frequency of IL28B CC genotype in this group. In the overall population, early virologic response was greater in patients with CC genotype, although this difference disappeared by week 12. Potentially, CC genotype may increase early viral suppression by increasing responsiveness to endogenous interferons that are released as a result of the rapid antiviral activity of the dual DAA therapy, allowing reversal of HCV-induced immunosuppression.[21]

These results in patients with HCV genotype 1b differ from those reported for genotype 1a. In a similar study of US/European null responders, 2/9 patients with genotype 1a achieved SVR with daclatasvir + asunaprevir dual therapy, compared with 10/10 patients with genotype 1a who received quadruple therapy combining daclatasvir and asunaprevir with alfa/RBV.[8] This difference suggests that viral genotype can influence responses to DAA regimens, and outcomes can be optimized by individualized therapy that considers viral genotype.

The two populations included in this study represent substantial numbers of patients worldwide. Approximately 10% of HCV genotype 1-infected patients receiving alfa/RBV have a null response.[22] The cumulative prevalence of alfa/RBV null responders and the frequent failure of retreatment with current regimens together suggest that a large population of null responders is awaiting improved therapies. The population of alfa/RBV ineligible or intolerant patients has not been studied extensively but may be substantial. In the IDEAL study, 23.2% of the 4469 patients

screened were considered ineligible for alfa/RBV therapy; of these, 30.3% had hematologic or psychiatric conditions that may not preclude DAA-only regimens.[23] In registration trials, 9.7% to 14% of patients receiving alfa/RBV discontinued study treatment due to intolerance.[24, 25] Moreover, these clinical trial data are likely to underestimate the true size of the ineligible and intolerant populations in community practice.

Virologic failures occurred relatively late in therapy after extended periods with undetectable HCV RNA. All seven patients with virologic failure had emergent NS5A and NS3 mutations that together confer high-level resistance to both daclatasvir and asunaprevir *in vitro*.[11, 12] Pretreatment, NS5A-Y93H was detected in five of the seven patients with virologic failure and in five additional patients who achieved SVR, suggesting that pre-existing Y93H is loosely associated with virologic failure but is not an absolute predictor. Pharmacokinetics may also have contributed; nearly all patients with virologic failure had trough plasma concentrations of daclatasvir and asunaprevir below their respective median values. However, SVR was achieved by most patients with trough drug levels below the median, and by several patients who discontinued study treatment after 2–16 weeks. Thus, the relationship of drug exposure to virologic outcome remains uncertain; further study is needed to define on-treatment predictors of outcome and the optimal duration of therapy.

Current data do not fully explain observed differences between the two study populations in rates of virologic failure and SVR. IL28B genotype was the primary difference between the two populations pretreatment. All three breakthroughs occurred in ineligible/intolerant patients with the unfavorable IL28B CT genotype; however, null responders had no breakthroughs despite a much higher frequency of this genotype. Pre-existing resistance-associated polymorphisms and

plasma drug concentrations were similar across populations, but only ineligible/intolerant patients experienced failure. Analysis of baseline parameters failed to identify other factors that may have influenced outcomes. However, these analyses were limited by the relatively small study population and may have been confounded by unreported non-adherence or baseline parameters not quantified absolutely, such as the stage of liver fibrosis. This issue requires further study in larger populations to confirm the apparent difference in outcomes and to identify factors predictive of virologic failure.

The adverse event profile of the study regimen was generally more favorable than that typically observed with alfa/RBV-containing regimens.[26] There were no significant hematologic or psychiatric abnormalities; the most common adverse events were non-specific in nature and generally mild to moderate in intensity. Mild diarrhea was experienced by 26% of study patients, consistent with previous studies of asunaprevir and other drugs of this class.[4, 6, 14] The four observed grade 3/4 ALT elevations resolved with continued therapy or after discontinuation and were not associated with significant clinical events. A role for study drugs in the reported serious adverse events cannot be ruled out except for the gastroenteritis; however, four of the six events resolved spontaneously with continued treatment. The case of hyperbilirubinemia with gastroenteritis was complicated by multiple confounding factors, and the contribution of study drugs is uncertain.[7]

In conclusion, dual oral therapy with daclatasvir and asunaprevir elicited rapid clearance of detectable HCV RNA and achieved high rates of SVR in two difficult-to-treat patient populations. These results confirm initial findings that HCV genotype 1b infections can be cured with daclatasvir combined with asunaprevir, without alfa/RBV.[7, 8] Thus, this regimen has potential to offer

effective treatment to null responders who have previously shown little or no response to alfa/RBV, and to alfa/RBV ineligible/intolerant patients who have no current treatment options. Further research will assess the benefits of this and other DAA combinations in larger and more diverse patient populations, but the promise of all oral and well-tolerated HCV therapy is on the horizon.

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FIGURE LEGENDS

Fig. 1. Patient disposition.

Patient flow through treatment and follow-up is shown. d/c, discontinuation of study medication; SVR_4, SVR_{12} and SVR_{24}, sustained virologic response 4, 12 or 24 weeks posttreatment. [a]On-study follow-up continued to posttreatment week 4; HCV RNA remained undetectable at posttreatment week 24 after study discontinuation, reported as failure for SVR_{24} per statistical protocol requirements; [b]HCV RNA was undetectable at posttreatment week 24 after study discontinuation due to addition of alfa/RBV, reported as failure for SVR per statistical protocol requirements; [c]On-study follow-up to assess SVR continued after discontinuation of study drugs.

Fig. 2. Outcomes by IL28B genotype.

Virologic outcomes at milestone time points are shown for the overall population by IL28B (rs12979860) genotype. End of treatment is week 24 or the last on-treatment visit for patients who discontinued early. RVR, rapid virologic response; cEVR, complete early virologic response; SVR_{12} and SVR_{24}, sustained virologic response 12 or 24 weeks posttreatment.

Fig. 3. HCV RNA levels, individual patients.

Serum HCV RNA levels over time are shown for each patient. Panel A, null responders; panel B, ineligible/intolerant patients. EOT, end of treatment; SVR_{24}, sustained virologic response 24 weeks posttreatment; LLOQ, lower limit of quantitation=15 IU/mL.

Fig. 4. Daclatasvir and asunaprevir trough plasma concentrations.

Available trough plasma concentrations of asunaprevir and daclatasvir for individual patients are plotted and color-coded according to each patient's virologic outcome. Multiple determinations are shown for some patients. *Indicates values from a single patient with documented noncompliance.

Figure 1

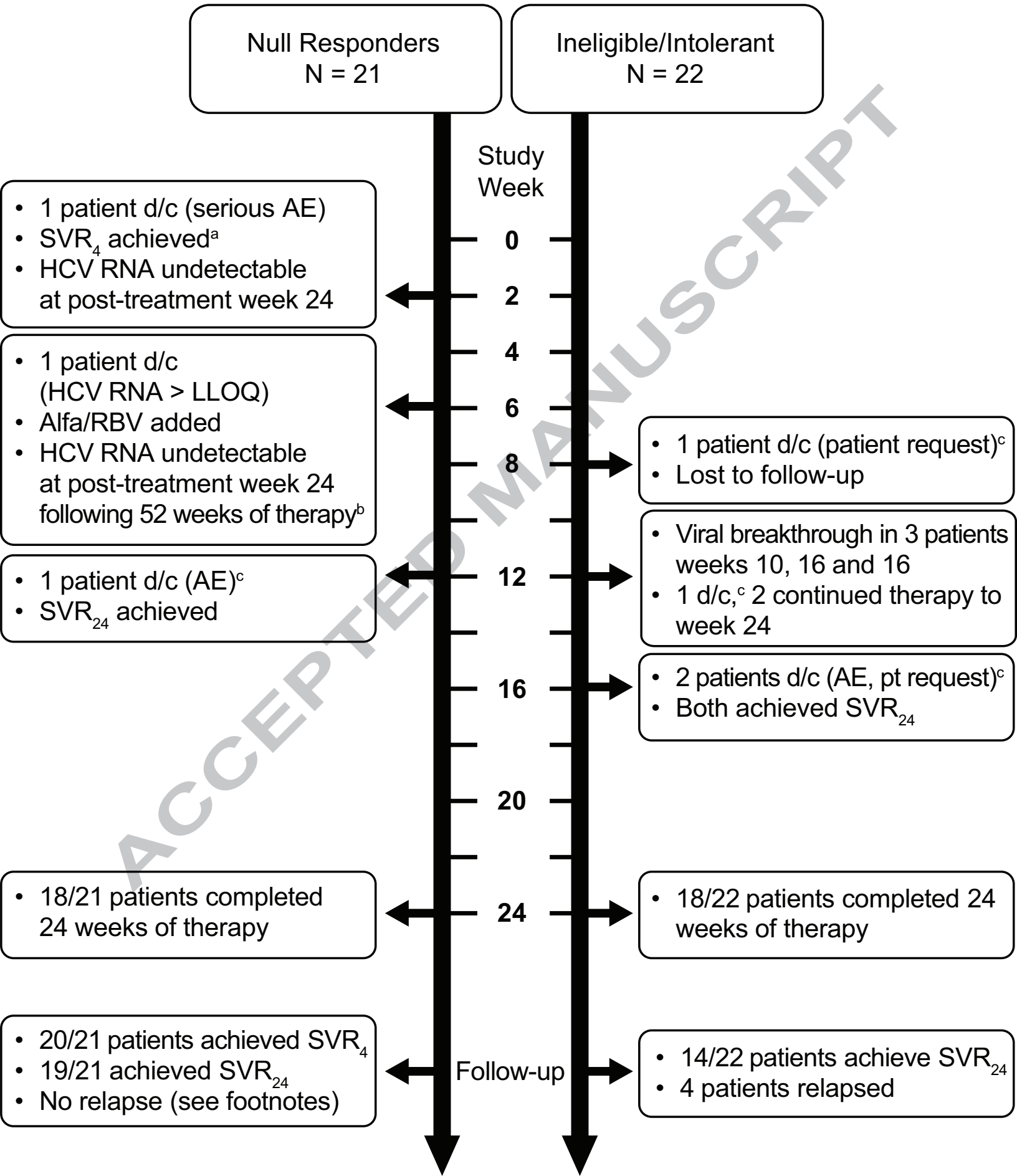


Figure 2

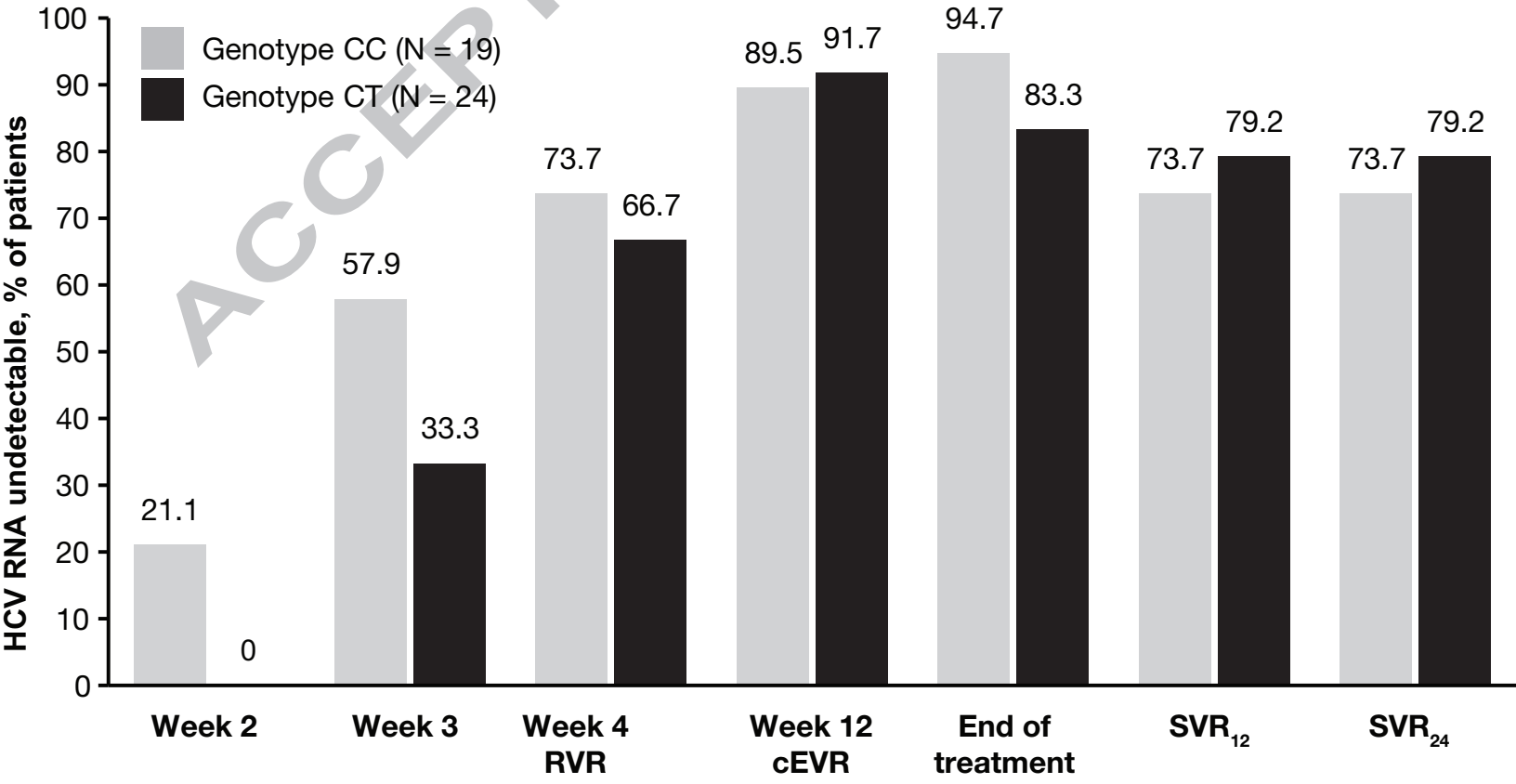
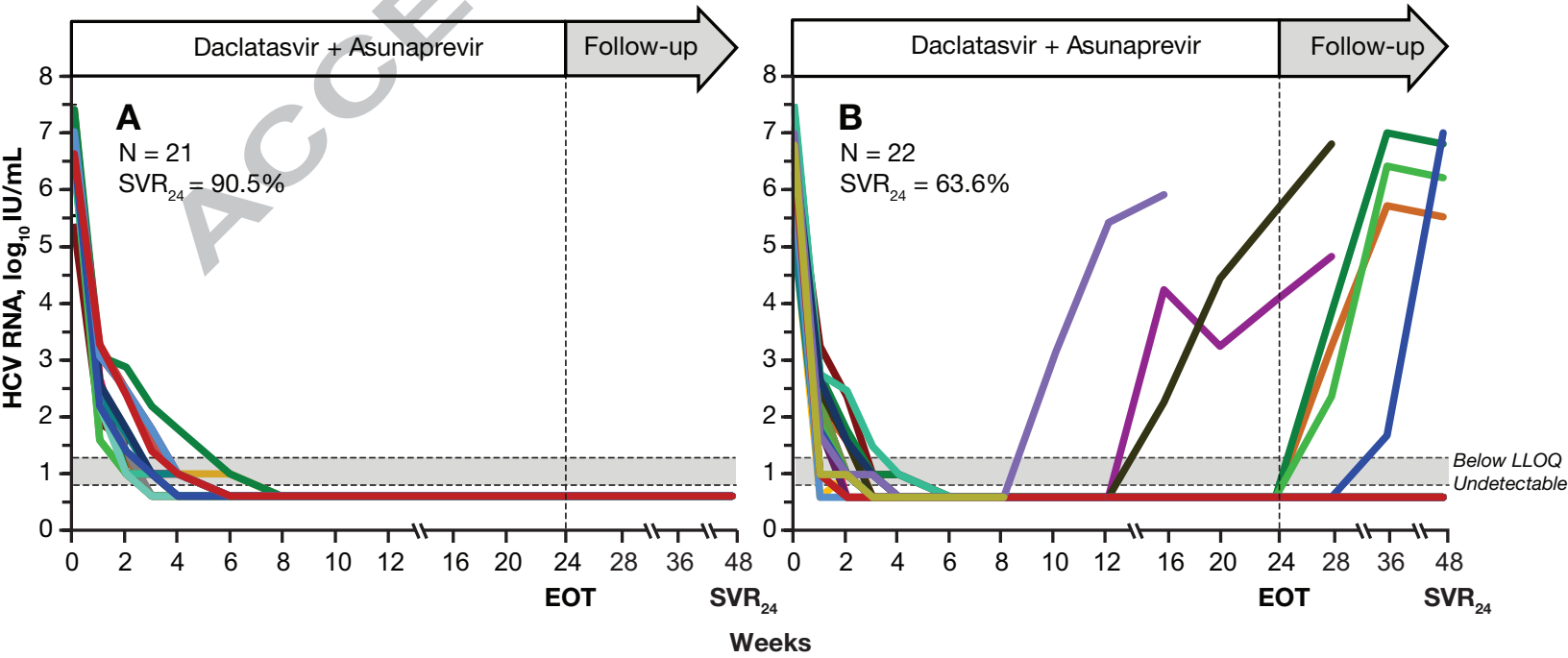
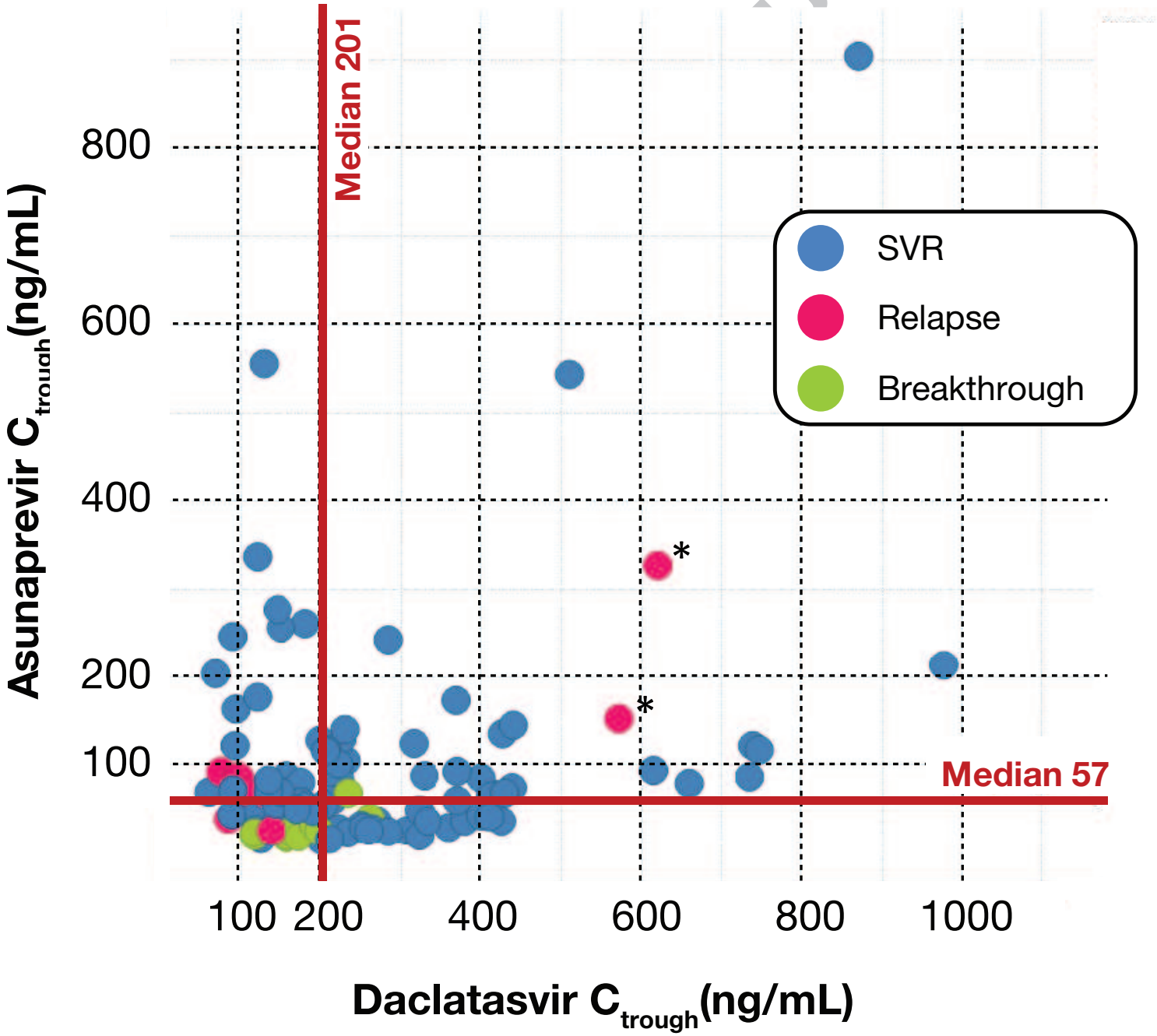


Figure 3



LLOQ, lower limit of quantitation = 15 IU/mL

Figure 4



TABLES

Table 1. Baseline demographic and disease characteristics

Parameter	Null Responders (N=21)	Ineligible/Intolerant (N=22)
Age, median years (range)	61 (31–70)	68 (47–75)
Male, n (%)	8 (38.1)	6 (27.3)
HCV genotype 1b, n (%)	21 (100)	22 (100)
IL28B genotype, n (%)		
(rs12979860) CT	18 (85.7)	6 (27.3)
CC	3 (14.3)	16 (72.7)
HCV RNA, mean $\log_{10}$ IU/mL (SD)	6.8 (0.47)	6.6 (0.64)
ALT, mean U/L (SD)	57.9 (24.86)	45.7 (25.79)
APRI score		
Score >2, n (%)	3 (14.3)	1 (4.5)
Median (range)	(0.24–3.41)	(0.40–2.79)
Alfa/RBV ineligible, n (%)	na	18 (81.8)
Alfa/RBV intolerant, n (%)	na	4 (18.2)

Table 2. Virologic outcomes

n (%)	Null Responders (N=21)	Ineligible/Intolerant (N=22)
HCV undetectable, week 4 (RVR)	11 (52.3)	19 (86.4)
HCV undetectable, week 12 (cEVR)	19 (90.5)	20 (90.9)
HCV undetectable, end of treatment	19 (90.5)	19 (86.4)
SVR_4	20 (95.2)[1]	15 (68.2)[2]
SVR_{12}	19 (90.5)[1]	14 (63.6)[2]
SVR_{24}	19 (90.5)[1]	14 (63.6)[2]
Viral breakthrough	0	3 (13.6)
Posttreatment relapse	0	4 (18.2)

Intention to treat (missing=failure) analysis. End of treatment is week 24 or last on-treatment visit for patients who discontinued early. RVR, rapid virologic response; cEVR, complete early virologic response; SVR_4, SVR_{12}, and SVR_{24}, sustained virologic response 4, 12 or 24 weeks posttreatment. [1]Two patients discontinued from the study before completion of follow-up. One patient received added alfa/RBV per protocol criteria and is counted as failure for SVR_4, SVR_{12}, and SVR_{24} for DAA-only therapy; one patient had missing HCV RNA data for follow-up weeks 12 and 24 and is counted as failure for SVR_{12} and SVR_{24} per statistical protocol. [2]One patient was lost to follow-up for assessment of SVR_{12} and SVR_{24}.

Table 3. Resistance-associated polymorphisms in patients with virologic failure

Patient			NS5A				NS3	
			L31	Q54	P58	Y93	Q80	D168
Viral Breakthrough	1	Baseline	L/M			Y/H		
		Post-VBT	M		A	H		A
	2	Baseline		Y		Y/H	L	
		Post-VBT	M	Y		H		V
	3	Baseline		Y		H		
		Post-VBT	M	Y		H		V
Posttreatment relapse	4	Baseline			P/S	Y/H		
		Post-relapse	M			H		A
	5	Baseline			L			
		Post-relapse	M		L	H		V/D
	6	Baseline						
		Post-relapse	V			H		V
	7	Baseline				H		
		Post-relapse	V/M			H		V

Table 4. Most frequent adverse events and laboratory abnormalities

Event, n (%)		Null Responders (N=21)	Ineligible/Intolerant (N=22)
Adverse Events Occurring in ≥ 3 Patients in Either Group	Headache	8 (38)	6 (27)
	Nasopharyngitis	6 (29)	8 (36)
	ALT increase	6 (29)	6 (27)
	Diarrhea	9 (43)	2 (9)
	AST increase	6 (29)	4 (18)
	Pyrexia	3 (14)	5 (23)
	Eosinophilia	1 (5)	4 (18)
	Abdominal discomfort	3 (14)	2 (9)
	Malaise	2 (10)	3 (14)
	Constipation	2 (10)	3 (14)
	Back pain	3 (14)	1 (5)
	Decreased appetite	0	3 (14)
Grade 3 or 4 Lab Abnormalities	ALT	2 (10)	2 (9)
	AST	1 (5)	2 (9)
	Lymphocytes	2 (10)	1 (5)
	Phosphorus	1 (5)	1 (5)
	Bilirubin, total	1 (5)	0

	Leukocytes	1 (5)	0