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Article type   : Original Paper

Efficacy and Safety of a Two-Drug Direct-Acting Antiviral Agent Regimen Ruzasvir 180 mg and Uprifosbuvir 450 mg for 12 Weeks in Adults with Chronic Hepatitis C Virus Genotype 1, 2, 3, 4, 5, or 6

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Running title: Ruzasvir/Uprifosbuvir for HCV Infection

These data were presented at The Liver Meeting® 2017; October 20-24, 2017; Washington, DC. Lawitz E et al. *Hepatology*. 2017;66(suppl):34A-35A.

Target journal: *Journal of Viral Hepatitis*

Word count: 4000 word limit (exc title page, refs, legends); current word count is 3994.

Tables / figures: Limit 6 figures / tables. Current draft has 3 tables and 3 figures.

Abbreviation List:

AEs - adverse events

ALT - alanine aminotransferase

APRI - aspartate aminotransferase to platelet ratio index

AST - aspartate aminotransferase

CI - confidence interval

DAAs - direct-acting antiviral agents

FAS - full analysis set

29   FW - follow-up week

30   GT - genotype

31   HCV - hepatitis C virus

32   HIV - human immunodeficiency virus

33   LLoQ - lower limit of quantitation

34   NS3/4A - nonstructural protein 3/4A

35   NS5A - nonstructural protein 5A

36   NS5B - nonstructural protein 5B

37   PP - per-protocol

38   RAP - resistance analysis population

39   RAS - resistance-associated substitution

40   SVR – sustained virologic response

41   SVR12 - sustained virologic response at 12 weeks after the completion of study therapy

42   TW - treatment week

43

44   **Abstract**

45   Ruzasvir (MK-8408, an NS5A inhibitor) and uprifosbuvir (MK-3682, a nonstructural protein 5B

46   nucleotide inhibitor) are highly potent direct-acting antiviral agents for the treatment of hepatitis

47   C virus (HCV) infection. A phase III clinical trial evaluating the two-drug combination of

48   ruzasvir 60 mg plus uprifosbuvir 450 mg suggested suboptimal efficacy in certain HCV

49   genotypes (C-BREEZE 1; NCT02759315). The aim of the present study was to evaluate the

50   efficacy and safety of rusasvir in combination with uprifosbuvir administered at a higher dose

51   than that assessed in the earlier study (C-BREEZE 2: NCT02956629 /Merck protocol PN041).

52   Treatment-naive or interferon (with or without ribavirin)–experienced participants with or

53   without compensated cirrhosis were enrolled. All participants received ruzasvir

54 180 mg plus uprifosbuvir 450 mg once daily for 12 weeks. The primary objectives were the

55 proportion of participants with HCV RNA <15 lU/mL at 12 weeks after the end of study therapy

56 (SVR12), and safety and tolerability of the study drug. Overall, 282 participants were enrolled.

57 SVR12 (n/N) was 91.3% (42/46) in participants infected with HCV genotype (GT) 1a; GT1b,

58 96.7% (29/30); GT2, 91.5% (43/47); GT3, 73.8% (45/61); GT4, 98.2% (55/56); GT5, 100.0%

59 (18/18); GT6, 90.9% (20/22). Adverse events (AEs) were reported by 61.3% of participants;

60 drug-related AEs were reported by 33.3%. The most frequent (≥5% of participants) drug-related

61 AEs in all participants were fatigue (7.8%) and headache (7.4%). In conclusion, the two-drug

62 combination of ruzasvir 180 mg plus uprifosbuvir 450 mg for 12 weeks was highly effective and

63 well-tolerated in participants infected with HCV GT1, GT2, GT4, GT5, and GT6, with a lower

64 efficacy in GT3-infected persons.

65

66 **Keywords:** hepatitis C virus; clinical trial; genotype; safety; efficacy

67 The development of direct-acting antiviral agents (DAAs) has transformed the treatment

68 of hepatitis C virus (HCV) infection,[1] and pangenotypic regimens are now available that result in

69 high rates of sustained virologic response (SVR) across all HCV genotypes (GT).[2] Treatment

70 options have transitioned from genotype-specific regimens such as sofosbuvir/ledipasvir,[3]

71 elbasvir/grazoprevir,[4] and paritaprevir/ombitasvir/ritonavir/dasabuvir[5] to pangenotypic regimens

72 such as glecaprevir/pibrentasvir [6] and sofosbuvir/velpatasvir.[7] An additional regimen under

73 investigation for pangenotypic activity is the combination of ruzasvir/uprifosbuvir.

74 Ruzasvir (MK-8408) is a potent HCV nonstructural protein 5A (NS5A) complex

75 inhibitor.[8] In vitro, it retains activity against RASs selected by first-generation NS5A inhibitors

76 in individuals infected with HCV GT1a.[8] Uprifosbuvir (MK-3682) is a potent HCV NS5B

77 polymerase nucleotide inhibitor with pangenotypic activity in vitro and a high barrier to

78 resistance. The safety and efficacy of ruzasvir, uprifosbuvir, and the nonstructural protein 3/4A

79 protease inhibitor grazoprevir was explored in the phase 2 C-CREST studies (ClinicalTrials.gov

80 numbers NCT02332707 and NCT02332720).[9-11] In these studies, the three-drug regimen of

81 ruzasvir 60 mg and uprifosbuvir 450 mg in combination with grazoprevir 100 mg, with or

82 without ribavirin, demonstrated high efficacy and excellent tolerability in a broad population that

83 included treatment-naive and prior interferon–experienced, cirrhotic and noncirrhotic

84   participants with HCV GT1-6 infection, and also participants who had experienced virologic

85   relapse after treatment with all-oral DAA regimens.[9-11] Given the high efficacy of

86   ruzasvir/uprifosbuvir/grazoprevir, the relative contribution of grazoprevir was evaluated in a

87   phase II nonrandomized study by evaluating the two-drug regimen of ruzasvir 60 mg and

88   uprifosbuvir 450 mg. Removal of grazoprevir would eliminate drug–drug interactions caused by

89   the NS3/4A protease inhibitor drug class, and would also eliminate concerns regarding hepatic

90   transaminase elevations with the protease inhibitor, thus potentially enabling use of the two-drug

91   regimen in a broader range of populations. In the C-BREEZE 1 study (NCT02759315), ruzasvir

92   60 mg and uprifosbuvir 450 mg was well tolerated but demonstrated lower efficacy for those

93   infected with GT3 and GT6 infection compared with those with GT1, GT2, or GT4 infection.[12] It

94   was hypothesized that a higher dose of ruzasvir might improve the efficacy of this regimen and

95   support a pangenotypic profile. In the present study, we evaluated the efficacy, safety, and

96   tolerability of the combination of ruzasvir 180 mg and uprifosbuvir 450 mg in participants with

97   HCV GT1-GT6 infection.

98

99   **METHODS**

100 *Study Design*

101 This was a phase II, nonrandomized, open-label clinical trial (ClinicalTrials.gov

102 identifier, NCT02956629/Merck protocol PN041). The study was conducted in accordance with

103 the Declaration of Helsinki and Good Clinical Practice guidelines. Independent institutional

104 review boards or ethics committees reviewed and approved the protocol and applicable

105 amendments for each institution, and all participants gave written informed consent. All

106 participants received ruzasvir 180 mg (3 × 60 mg capsules) plus uprifosbuvir 450 mg (3 × 150

107 mg tablets) orally once daily as separate medications administered under fasting conditions for

108 12 weeks. Dose modifications were not permitted during the study.

109 After the first 50 participants of any HCV GT were allocated to treatment, allocation was

110 paused to assess general safety and tolerability at treatment week (TW) 4. When general safety

111 and tolerability were assessed to be acceptable, the subsequent 200 participants were allocated to

112 treatment with an overall stratification based on genotype. The first 50 participants were included

113 in the overall treatment allocation target of the trial.

114

Participants

Adults aged ≥18 years with chronic HCV GT1-6 infection were enrolled. Participants were either treatment-naive or had experienced virologic failure following treatment with an interferon-containing treatment regimen. Participants with fibrosis stage F0-F4 were eligible; cirrhosis was defined as a liver biopsy study consistent with METAVIR F4, FibroScan® performed within 12 months with a result of >12.5 kPa, or a FibroSure® (FibroTest®) performed during screening with a score of >0.75 and an aspartate aminotransferase (AST) to platelet ratio index (APRI) of >2. Among those infected with HCV GT1-GT4, the allocation target was 25%-30% individuals with cirrhosis. Participants could also be either HCV-monoinfected or coinfected with HCV and human immunodeficiency virus (HIV). Participants receiving HIV medications other than tenofovir, abacavir, lamivudine, emtricitabine, raltegravir, dolutegravir, or rilpivirine were excluded.

Participants who had previously received a DAA-based treatment regimen, with hepatitis B virus coinfection (defined as hepatitis B surface antigen–positive), with evidence of decompensated liver disease (presence or history of ascites, esophageal or gastric variceal bleeding, hepatic encephalopathy), with Child-Pugh class B or C cirrhosis (a Child-Pugh-Turcotte score >6), or with evidence of hepatocellular carcinoma were excluded. Participants with alanine aminotransferase (ALT) or AST >10× upper limit of normal, hemoglobin <10 g/dL, platelets <50 × 10³/μL, serum albumin <3.0 g/dL, international normalized ratio >1.7 (unless stable on anticoagulant regimen), or estimated glomerular filtration rate <50 mL/min/1.73 m² were also excluded.

End points

The primary efficacy end point was sustained virologic response at 12 weeks after the completion of therapy (SVR12). HCV RNA was assessed using the Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Test v2.0 with a lower limit of quantitation (LLoQ) <15 IU/mL. Virologic relapse was defined as HCV RNA ≥LLoQ following completion of all study therapy, after becoming undetectable at end of treatment. Secondary end points included the proportion of participants with virologic failure.

145 Safety and tolerability were assessed through the clinical evaluation of adverse events (AEs),

146 vital signs, physical examinations, electrocardiograms, and standard laboratory safety tests.

147

148 Resistance analyses were conducted in all participants with available sequencing data and a

149 treatment outcome of SVR12 or virologic failure (resistance analysis population; RAP). The

150 prevalence and impact on SVR12 of baseline RASs in the NS5A and NS5B regions were

151 assessed using next-generation sequencing (15% sensitivity threshold). NS5A substitutions at

152 amino acid positions 28, 30, 31, or 93 were assessed in all participants. In addition, NS5A RASs

153 at position 58 were assessed in participants with HCV GT3, GT4, or GT6 infection, and RASs at

154 positions 24 or 62 were assessed in participants with GT3 infection. Regardless of HCV

155 genotype, participants who experienced virologic failure had baseline samples sequenced for

156 NS5A RASs at positions 24, 28, 30, 31, 58, 62, or 93. NS5B substitutions at amino acid

157 positions 159, 239, 282, 316, 320, or 321 were also assessed for all genotypes.

158

159 *Statistics*

160 Planned enrollment was approximately 250 participants, with an allocation target of 50

161 participants with HCV GT1 infection, 50 with GT2 infection, 50 with GT3 infection, 50 with

162 GT4 infection, and 25 each with GT5 and GT6 infection. The sample size was based on practical

163 considerations that enabled a reasonable estimation of the SVR12 for each genotype. The full

164 analysis set (FAS) population included all participants who received at least one dose of study

165 drug; in this study, the safety population is identical to the FAS. The per-protocol (PP)

166 population excluded participants who discontinued treatment for administrative reasons (lost to

167 follow-up, withdrew consent). However, participants who discontinued treatment because of

168 drug-related AEs were included in the PP population and counted as treatment failures, and any

169 participant categorized as a reinfection was considered a success in the PP population. The RAP

170 excluded participants who discontinued for reasons other than virologic failure.

171

172

173 **Results**

174 In total, 329 people were screened, and 282 participants were enrolled between November 2016

175 and June 2017. Most participants were male (55.3%); median age was 51.0 years; 78.4% were

176 white; 27.7% had HCV GT1 infection (GT1a, n=46; GT1b, n=30; GT1-other, n=2); 21.6%

177 (n=61) had GT3 infection; 73.0% had baseline HCV RNA >800,000 IU/mL; 20.6% were

178 cirrhotic; 84.0% were treatment-naive; and 3.9% were HCV/HIV co-infected (**Table 1**). Nearly

179 all participants (273/282, 96.8%) received at least one dose of study medication and completed

180 the follow-up week (FW) 12 visit (**Figure 1**).

181

182 *SVR*

183 The SVR12 rate was 89.7% (n/N=253/282; 95% confidence interval [CI], 85.6%-93.0%) in the

184 FAS population. Twenty-nine participants did not achieve SVR12; of these, 19 experienced

185 virologic relapse, 2 experienced drug-related AEs, 1 had reinfection, and 7 participants

186 discontinued for non-study medication-related reasons. In the PP population, the SVR12 was

187 92.3% (251/272; 88.4%-95.2%) (**Table 2**).

188   The SVR12 rate in participants with HCV GT1a infection was 89.6% (43/48; 95% CI

189 77.3%-96.5%) (**Table 2**). Of the five participants with GT1a infection who failed to achieve

190 SVR12, two discontinued from the trial (one participant withdrew from study medication prior to

191 TW2 owing to an AE of substance abuse, and one participant withdrew from the trial prior to

192 TW4) and three relapsed. Of those who relapsed, two relapsed at FW4 and one relapsed at FW12

193 with GT1l that was categorized as GT1a for the analysis. SVR12 appeared to be unaffected by

194 cirrhosis status, with SVR12 rates of 88.9% (8/9) and 97.1% (33/34) in cirrhotic and non-

195 cirrhotic participants, respectively (**Table 3**; FAS population is summarized in **Supplementary**

196 **Table 1**). SVR12 in participants infected with GT1b infection was 96.7% (29/30; 81.8%-99.9%)

197 (**Table 2**). The only participant with GT1b infection who failed to achieve SVR12 was lost to

198 follow-up at FW4. SVR12 was unaffected by cirrhosis status: 100% (7/7) in cirrhotic participants

199 and 100.0% (22/22) in non-cirrhotic participants, although the number of cirrhotic participants

200 was low (**Table 3**; **Supplementary Table 1**).

201   SVR12 was 91.5% (43/47; 95% CI, 79.6%-97.6 %) in participants with HCV GT2

202 infection (**Table 2**). Among the four participants with GT2 who failed to achieve SVR12, one

203 experienced virologic relapse at FW8. The site reported significant non-compliance with study

204 medication dosing for this participant, who took each dose of medication with food and had

205 confirmed low drug exposure. The other three participants who failed to achieve SVR12 all

206 discontinued from the trial: one discontinued owing to drug-related AEs of insomnia and fatigue

207 prior to TW6, and two were lost to follow-up after FW8. SVR12 was 100% (10/10) in cirrhotic

208 participants and 94.1% (32/34) in non-cirrhotic participants, and was unaffected by baseline

209 HCV RNA (94.1% [16/17] in those with baseline HCV RNA ≤2,000,000 IU/mL and 96.3%

210 [26/27] in those with baseline HCV RNA >2,000,000 IU/mL) (**Table 3**; **Supplementary Table**

211 **1**).

212   SVR12 rates were the lowest in participants with HCV GT3 infection (73.8%; 45/61;

213 95% CI 60.9%-84.2%) (**Table 2**). Of the 16 participants with GT3 infection who failed to

214 achieve SVR12, 1 had evidence of reinfection at FW8 (GT3 at baseline and GT1a at FW8), 1

215 discontinued from the trial owing to a non–drug-related AE of substance abuse prior to TW4,

216 and 14 relapsed (12 by FW4 and 2 by FW8). SVR12 was 68.4% (13/19) in cirrhotic participants

217 with HCV GT3 infection and 80.0% (32/40) in non-cirrhotic participants, and was 91.3% (21/23)

218 in those with baseline HCV RNA ≤2,000,000 IU/mL and 66.7% (24/36) in those with baseline

219 HCV RNA >2,000,000 IU/mL (**Table 3**; **Supplementary Table 1**).

220   The SVR12 rate was 98.2% (55/56; 95% CI, 90.4%-100.0%) in participants with HCV

221 GT4 (**Table 2**). The one participant with HCV GT4 infection who failed to achieve SVR12

222 discontinued study medication owing to a non–drug-related AE of abdominal pain prior to TW6.

223 In the PP population, the SVR12 rate was 100% regardless of cirrhosis status or baseline HCV

224 RNA (**Table 3**; **Supplementary Table 1**).

225   SVR12 was 100% in participants with HCV GT5 infection (18/18; 95% CI, 84.7%-

226 100.0%) and 90.9% (20/22; 95% CI,70.8%-98.9%) in those with GT6 infection (**Table 2**). Two

227 participants infected with HCV GT6 failed to achieve SVR12: one relapsed at FW4 and the other

228 discontinued study medication prior to Day 7 because of the drug-related AEs of anxiety and

229 nausea. In participants with GT6 infection, the SVR12 rate was 100% (4/4) in those with

230 cirrhosis and 88.9% (16/18; 65.3%-98.6%) in those without cirrhosis, and 88.9% (8/9) in

231 participants with baseline HCV RNA ≤2,000,000 IU/mL and 92.3% (12/13) in those with

232 baseline HCV RNA <2,000,000 IU/mL (**Table 3**; **Supplementary Table 1**).

233   Compared with SVR12 data for the FAS population, two participants (both with GT6

234 infection) relapsed between FW12 and FW24.

235

236 *Efficacy by baseline NS5A RASs*

237   The prevalence of baseline NS5A RASs varied according to HCV genotype, ranging from 0.0%

238   among those infected with HCV GT5 to 86.4% among those infected with HCV GT2, where the

239   majority of these (32/38) were 31L/M (**Supplementary Table 2**). Among those with GT1a

240   infection, the presence of NS5A RAS impacted efficacy (84.6% [11/13] vs 100.0% [31/31] in

241   those with and without RASs, respectively). (**Figure 2**) When efficacy was evaluated according

242   to RAS position, lower efficacy was observed only in the two participants with GT1a infection

243   who had Y93 baseline RAS; one participant had a single Y93 substitution at baseline and the

244   other had substitutions at Y93 and Q30L.

245

246   Efficacy for participants with GT1b (n=29) and GT4 (n=54) was not impacted by the presence of

247   NS5A RASs; SVR12 was 100.0% regardless of the presence of RASs (**Figure 2**). Similarly,

248   detectable NS5A RASs did not significantly impact efficacy in those with HCV GT2 infection

249   (SVR12 rates were 97.4% [37/38] and 100.0% [6/6] for those with and without RASs,

250   respectively) (**Figure 2**); the one participant who relapsed had baseline NS5A 31M RAS.

251

252   SVR12 rates were lower in participants with HCV GT3 infection and NS5A RASs at baseline

253   compared with those with no RASs at baseline (70% [21/30] vs 86.2% [25/29]) (**Figure 2**). The

254   lower efficacy in GT3-infected participants with baseline RASs was not clearly associated with

255   any specific RAS (**Figure 3**).

256

257   All 18 participants with HCV GT5 infection achieved SVR12 (100%; 18/18); none of these

258   participants had detectable NS5A RASs (**Figure 2**). Finally, the rate of SVR12 was 90.9%

259   (10/11) for those with GT6 infection without detectable NS5A RASs and 100.0% (9/9) for those

260   with detectable substitutions (**Figure 2**).

261

262   *Efficacy by baseline NS5B RASs*

263   The prevalence of baseline NS5B RASs varied among persons in the RAP depending on

264   HCV genotype, ranging from 0.0% among those infected with HCV GT1a, GT3, GT5, or GT6 to

265   24.1% among those infected with GT1b (**Supplementary Table 2**). There was no impact of

266   baseline NS5B RAS on efficacy across genotypes. All participants with baseline NS5B RASs

267 achieved SVR12 (9/9; 100%) compared with 92.9% (234/252) of participants without baseline
268 NS5B RASs.
269
270 *Treatment-emergent RASs*
271   Both of the participants with HCV GT1a infection who relapsed had RASs in the NS5A
272 gene region at baseline; one had substitutions at Y93C, and one at Q30L, H58L, and Y93H. The
273 participant with baseline Y93C had two treatment-emergent substitutions: L31V and Y93H. The
274 other participant had two additional substitutions at failure: the addition of L31V and the further
275 diversity of position 58 (52% L, 46% P). The participant with GT1l infection who relapsed had a
276 baseline R30Q RAS, and an additional treatment-emergent Y93H at failure. The one participant
277 with GT2 infection who experienced virologic failure had a baseline RAS in the *NS5A* gene
278 region at T24A and L31M, and no substitutions in the *NS5B* gene region. These substitutions
279 were also present at failure, and no treatment-emergent RASs were detected. The one participant
280 with HCV GT6e infection who relapsed at FW4 did not have detectable baseline RAS; but had
281 treatment-emergent L31M and T93S at the time of relapse. Among the two other participants
282 with GT6 infection who relapsed at FW24, one was GT6q and one was GT6e; neither had any
283 RASs at NS5A or NS5B at baseline or at the time of relapse.
284   Fourteen participants infected with HCV GT3 had a virologic relapse; 11/14 relapsed by
285 FW4, 2/14 by FW8, and 1 at FW12. Four participants did not have RASs at baseline but had
286 treatment-emergent Y93H at relapse; one of the four also had treatment-emergent S62T. Eight
287 participants had RASs at position S62 at baseline (S62T, n=5; S62M, n=1; S62V, n=1; S62I,
288 n=1); the participant with S62I also had A30S and Y93H at baseline, and one participant with
289 S62T also had a Y93H at baseline. All five participants with S62T at baseline also had S62T at
290 relapse; 3/5 also had treatment-emergent Y93H at relapse, 1/5 had Y93H at baseline and relapse,
291 and 1/5 had treatment-emergent L31F RAS. The participant with A30S, S62I, and Y93H at
292 baseline had the same RASs at relapse. The participant with an S62M RAS at baseline had
293 treatment-emergent S62V/Y93H at relapse, and the participant with S62V at baseline had
294 S62V/Y93H RASs at relapse. The two other participants with GT3 infection who relapsed had
295 A30M/A30K/Y93H and A30K at baseline, and A30K/Y93H and A30K/L31V at relapse (both at
296 FW4).

297   Treatment-emergent NS5B RASs were observed in one participant with HCV GT3

298   infection. This participant did not have any NS5A or NS5B RASs detected at baseline, and

299   experienced virologic failure at FW8 with treatment-emergent Y93H in the *NS5A* gene region

300   and S282T RAS in the *NS5B* gene region; however, no NS5B RASs were detected in this region

301   at FW12 and FW24.

302

303   *Safety*

304   The majority of participants reported at least one AE (173/282; 61.3%); the most common AEs

305   (reported in ≥5%) were headache (n=33, 11.7%), fatigue (n=29, 10.3%), nausea (n=19, 6.7%),

306   and diarrhea (n=14, 5.0%). Drug-related AEs were reported by 94 participants (33.3%); the most

307   common were fatigue (n=22, 7.8%) and headache (n=21, 7.4%). Seven (2.5%) participants

308   reported 12 serious AEs during the trial (1 each of acute coronary syndrome, diarrhea, abscess

309   limb, cellulitis, sinusitis, fall, rhabdomyolysis, acute kidney injury, increased ammonia level,

310   increased blood creatinine level, decreased glomerular filtration rate, and ovarian cyst), none of

311   which were assessed to be drug-related. Five participants (1.8%) reported AEs leading to

312   discontinuation of study medication, including substance abuse (n=2), anxiety and nausea (n=1),

313   insomnia and fatigue (n=1), and abdominal pain (n=1); two (0.7%) of these were considered

314   drug-related AEs (anxiety and nausea; insomnia and fatigue).

315   Two participants experienced hepatic events of clinical interest, defined as the first

316   instance of ALT or AST >500 IU/L, or ALT or AST >3× nadir and >3× the upper limit of

317   normal (ULN) from the initiation of study therapy through the first 14 days of follow-up. One

318   participant had an asymptomatic elevation of AST (153 U/L) at TW4 associated with an elevated

319   creatine phosphokinase level. One participant sustained a fall with resultant rhabdomyolysis that

320   was reported as a serious AE not related to study medication, and the associated elevated ALT

321   met criteria for a hepatic event of clinical interest. This same participant met criteria for a renal

322   event of clinical interest, defined as the first instance of an estimated glomerular filtration rate

323   <50 mL/min/1.73 m^2 from the initiation of study therapy through 14 days following treatment, or

324   the first instance of serum creatinine grade 2 or higher (>1.3 × ULN) and elevated from baseline

325   from the initiation of study therapy through 14 days following treatment.

326

327

Discussion

The combination of ruzasvir 180 mg and uprifosbuvir 450 mg for 12 weeks was generally well tolerated. High efficacy was observed in participants with HCV GT1, GT2, GT4, GT5, and GT6 infection, with lower efficacy in those with GT3 infection. Although the number of participants was small, the study results suggest a potential impact of baseline NS5A Y93 RAS in persons with GT1a. Efficacy was not affected by cirrhosis status or RASs in those with GT1b, GT2, GT4, and GT5 infection. Efficacy was lower in participants infected with HCV GT3 regardless of cirrhosis status and was only partially accounted for by baseline NS5A RASs.

The C-BREEZE-1 trial of ruzasvir 60 mg plus uprifosbuvir 450 mg did not show pangenotypic activity; SVR12 rates were high among those with HCV GT1a (96%; 52/54), GT1b (100%; 15/15), GT2 (97% 28/29), and GT4 infection (90%; 18/20), with lower efficacy in those with GT3 (77%; 33/39) and GT6 infection (67%; 2/3).[12] In the phase II C-CREST trials, the three-drug regimen of ruzasvir 60 mg and uprifosbuvir 450 mg in combination with grazoprevir 100 mg, with or without ribavirin, resulted in SVR12 rates of >90% in a broad patient population with HCV GT1, GT2, GT3, GT4, or GT6 infection.[9,10] It was hypothesized that a higher dose of ruzasvir might improve pangenotypic activity of the ruzasvir and uprifosbuvir combination and compensate for the lack of NS3/4A inhibition provided by grazoprevir in the C-CREST trials. In the current trial of uprifosbuvir 450 mg and the higher dose of ruzasvir 180 mg, SVR12 rates in the FAS population were not meaningfully higher than those observed with the lower dose of ruzasvir 60 mg in combination with uprifosbuvir.

In the current trial, we hypothesized that an increased dose of ruzasvir would overcome the lower efficacy in individuals with HCV GT3 infection observed in C-BREEZE-1.[12] However, we observed that the ruzasvir 180 mg dose used in the present study did not result in higher efficacy in participants with GT3 infection compared with the 60-mg dose of ruzasvir used in C-BREEZE-1 (SVR12 rates of 77% and 73.8%, respectively).[12] It is possible that a plateau was reached on the dose-response curve such that increasing the dose of ruzasvir did not result in any increase in efficacy for GT3 infection. The larger number of participants with GT6 infection who were enrolled in C-BREEZE-2 enabled us to more thoroughly evaluate efficacy in this population compared with C-BREEZE-1 (90.9% [20/22] vs 67% [2/3]). Although there was no appreciable difference in SVR12 rates between the lower and the higher ruzasvir doses used

358 in C-BREEZE-1 and C-BREEZE-2, a difference was seen between the ruzasvir plus uprifosbuvir

359 two-drug combination regimen and the ruzasvir-uprifosbuvir-grazoprevir triple-drug regimen

360 evaluated in the C-CREST studies,[9-11] suggesting that for the particular combination of ruzasvir

361 and uprifosbuvir, a third drug is required to ensure a pangenotypic profile. A three-drug

362 combination including uprifosbuvir, grazoprevir, and ruzasvir at the higher dose of 180 mg of

363 ruzasvir has not been evaluated.

364 In the C-BREEZE-1 trial, lower efficacy was observed in cirrhotic participants; 10 of 13

365 participants who relapsed had cirrhosis, including 6 of 9 participants with HCV GT3 infection

366 (67%).[12] Coupled with an analysis of RASs, the data from C-BREEZE-1 suggested that infection

367 with HCV GT1a, GT3, or GT6 in participants who were cirrhotic and/or had baseline RASs was

368 associated with lower SVR rates after treatment with ruzasvir 60 mg plus uprifosbuvir 450 mg.[12]

369 In the current analysis, SVR12 rates in the GT3 subtype were 68.4% (13/19) in cirrhotic

370 participants and 80.0% (32/40) in noncirrhotic participants (PP population). However, 57.1%

371 (8/14) of GT3-infected participants in the PP population with virologic failure were noncirrhotic,

372 suggesting that cirrhosis status may not have as clinically relevant an impact on SVR12 as

373 previously hypothesized.

374 Historically, the presence of RASs at baseline has been associated with lower SVR12

375 rates with some DAA regimens. In our trial, all three participants with HCV GT1 infection who

376 experienced virologic failure (GT1a, n=2; GT1l, n=1) had baseline RASs (Y93C, Q30L/ Y93H,

377 and R30Q, respectively). Participants with HCV GT3 infection who experienced virologic

378 failure were likely to have NS5A RASs at baseline (71.4%; 10/14) and at relapse (100%; 14/14),

379 which is in contrast to the results of the C-BREEZE-1 trial, where two of nine participants with

380 GT3 infection who relapsed had baseline NS5A RASs.[12] The most common baseline NS5A RAS

381 in GT3-infected participants was at S62 (57.1%; 8/14), and the most common treatment-

382 emergent RAS was Y93H (71.4% 10/14). The presence of Y93H at baseline has previously been

383 shown to impact the efficacy of DAAs, while the double RAS combinations A30K + L31M and

384 A30K + Y93H and the triple combination A30K + L31M + Y93H have been shown to severely

385 impact susceptibility to daclatasvir, velpatasvir, and elbasvir and to modestly impact

386 susceptibility to pibrentasvir.[13] It has also been shown that S62 substitutions, while not directly

387 impacting the SVR rate achieved with daclatasvir, may modify the effects of other RASs.[14] Of

388 note, 75% (6/8) of HCV GT3–infected participants with baseline S62 RASs had treatment-
389 emergent RASs: five had treatment-emergent Y93H and one had treatment-emergent L31F.
390 While single S62 substitutions cause minimal (0.2 to 20-fold) shifts in the ruzasvir EC_{50} in vitro,
391 the presence of additional RASs on the same genome can result in substantial potency losses.
392 The combination of S62I/L/T and Y93H in the GT3 replicon conferred potency losses >1000-
393 fold to ruzasvir. Thus, selection of the treatment-emergent RASs in addition to the baseline S62
394 substitutions impacted ruzasvir potency in those virologic failures.

395   Interpretation of this analysis is subject to several limitations. The size of each genotype
396 population was small, limiting the precision of efficacy measures. This is particularly notable for
397 subpopulations with baseline RASs. The study also had limited enrollment of potentially
398 important subpopulations, such as black participants and those co-infected with HCV/HIV.
399 Finally, there was no direct comparison to either standard-of-care DAA regimens nor to ruzasvir
400 60 mg plus uprifosbuvir 450 mg in the same trial.

401   In conclusion, data from the present study indicate that the combination of ruzasvir 180
402 mg plus uprifosbuvir 450 mg once daily for 12 weeks was well tolerated overall but was
403 suboptimal as a pangenotypic regimen.

404

405 **Statement of Interests**

416   Maria Buti has received personal fees from MSD, Gilead, and AbbVie.

417   Graham R. Foster has received grant and personal fees from MSD, Gilead, and AbbVie.

418   Krzysztof Tomasiewicz has received grants, personal fees, and non-financial support from
419   Gilead, AbbVie, and BMS and personal fees and non-financial support from MSD.

420   Frederick Lahser, Beth Jackson, Stephanie Klopfer, Melissa Shaughnessy, Wendy W. Yeh,
421   Michael N. Robertson, George J. Hanna, Eliav Barr, and Heather Platt are employees of MSD.

422   Stephanie Klopfer, Melissa Shaughnessy, Wendy W. Yeh, Michael N. Robertson, George J.
423   Hanna, Eliav Barr, and Heather Platt may own stock in Merck & Co., Inc., Kenilworth, NJ,
424   USA.

425   The following authors have nothing to disclose: Mordechai Rabinovitz, Eduard Z. Burnevich,
426   Helena Katchman.

427

428   **Author Contributions**

429   Eric Lawitz contributed to the acquisition of the data, interpretation of the results, and critically
430   reviewing and revising the manuscript for important intellectual content. Edward Gane
431   contributed to the acquisition of the data, interpretation of the results, and critically reviewing
432   and revising the manuscript for important intellectual content. Jordan J. Feld contributed to the
433   conception, design, and planning of the study, interpretation of the results, and critically
434   reviewing and revising the manuscript for important intellectual content. Maria Buti contributed
435   to the acquisition of the data, analysis of the data, interpretation of the results, drafting of the
436   manuscript, and critically reviewing and revising the manuscript for important intellectual
437   content. Graham R. Foster contributed to the conception, design, and planning of the study,
438   acquisition of the data, analysis of the data, interpretation of the results, and critically reviewing
439   and revising the manuscript for important intellectual content. Mordechai Rabinovitz contributed
440   to the acquisition of the data and critically reviewing and revising the manuscript for important
441   intellectual content. Eduard Burnevich contributed to the acquisition of the data and critically
442   reviewing and revising the manuscript for important intellectual content. Helena Katchman
443   contributed to the acquisition of the data and drafting of the manuscript. Krzysztof Tomasiewicz

444 contributed to the acquisition of the data and critically reviewing and revising the manuscript for
445 important intellectual content. Fred Lahser contributed to the interpretation of the results and
446 critically reviewing and revising the manuscript for important intellectual content. Beth Jackson
447 contributed to the conception, design, and planning of the study, analysis of the data,
448 interpretation of the results, and drafting of the manuscript. Melissa Shaughnessy contributed to
449 the conception, design, and planning of the study, acquisition of the data, analysis of the data,
450 and critically reviewing and revising the manuscript for important intellectual content. Stephanie
451 Klopfer contributed to the conception, design, and planning of the study, analysis of the data,
452 interpretation of the results, and critically reviewing and revising the manuscript for important
453 intellectual content. Wendy W. Yeh contributed to the conception, design, and planning of the
454 study, interpretation of the results, drafting of the manuscript, and critically reviewing and
455 revising the manuscript for important intellectual content. Michael N. Robertson contributed to
456 the conception, design, and planning of the study, interpretation of the results, and critically
457 reviewing and revising the manuscript for important intellectual content. George J. Hanna
458 contributed to the analysis of the data, interpretation of the results, and critically reviewing and
459 revising the manuscript for important intellectual content. Eliav Barr contributed to the
460 conception, design, and planning of the study, analysis of the data, interpretation of the results,
461 drafting of the manuscript, and critically reviewing and revising the manuscript for important
462 intellectual content. Heather L. Platt contributed to the conception, design, and planning of the
463 study, acquisition of the data, analysis of the data, interpretation of the results, drafting of the
464 manuscript, and critically reviewing and revising the manuscript for important intellectual
465 content.
466

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503   sofosbuvir, with or without ribavirin. *Antivir Ther.* 2017;22(3):237-246.

504

505   **SUPPORTING INFORMATION**

506 Additional Supporting Information may be found online in the supporting information tab for
507 this article.

508

509

510 **TABLE 1** Baseline patient demographics.

Characteristic	HCV genotype						All participants N=282
	GT1 n=78	GT2 n=47	GT3 n=61	GT4 n=56	GT5 n=18	GT6 n=22	
Sex, n (%)							
Male	43 (55.1)	23 (48.9)	34 (55.7)	33 (58.9)	7 (38.9)	16 (72.7)	156 (55.3)
Female	35 (44.9)	24 (51.1)	27 (44.3)	23 (41.1)	11 (61.1)	6 (27.3)	126 (44.7)
Age, median (range), years	49.5 (19-69)	54.0 (27-73)	51.0 (26-67)	48.0 (23-81)	57.5 (29-74)	57.5 (33-69)	51.0 (19-81)
Race, n (%)							
Asian	2 (2.6)	2 (4.3)	2 (3.3)	0 (0)	1 (5.6)	22 (100.0)	29 (10.3)
Black	4 (5.1)	0 (0)	1 (1.6)	8 (14.3)	9 (50.0)	0 (0)	22 (7.8)
Multiple	1 (1.3)	0 (0)	1 (1.6)	0 (0)	4 (22.2)	0 (0)	6 (2.1)
Native Hawaiian or other Pacific Islander	2 (2.6)	1 (2.1)	0 (0)	1 (1.8)	0 (0)	0 (0)	4 (1.4)
White	69 (88.5)	44 (93.6)	57 (93.4)	47 (83.9)	4 (22.2)	0 (0)	221 (78.4)
Ethnicity, n (%)							
Hispanic/Latino	13 (16.7)	14 (29.8)	12 (19.7)	0 (0)	0 (0)	0 (0)	39 (13.8)

Not Hispanic or Latino	64 (82.1)	32 (68.1)	49 (80.3)	54 (96.4)	18 (100.0)	22 (100.0)	239 (84.8)
Not reported	1 (1.3)	1 (2.1)	0 (0)	2 (3.6)	0 (0)	0 (0)	4 (1.4)
Body-mass index							
kg/m^2, median (range)	26.8 (14.2-42.6)	27.5 (18.9-50.4)	27.4 (17.1-41.6)	25.3 (18.9-35.7)	30.2 (17.3-40.3)	24.8 (17.3-30.1)	26.8 (14.2-50.4)
≥30 kg/m^2, n (%)	22 (28.2)	14 (29.8)	18 (29.5)	11 (19.6)	9 (50.0)	1 (4.5)	75 (26.6)
Baseline HCV RNA, n (%)							
>800,000 IU/mL	59 (75.6)	34 (72.3)	45 (73.8)	39 (69.6)	14 (77.8)	15 (68.2)	206 (73.0)
>2,000,000 IU/mL	44 (56.4)	29 (61.7)	36 (59.0)	24 (42.9)	11 (61.1)	13 (59.1)	157 (55.7)
Cirrhosis, n (%)	17 (21.8)	10 (21.3)	20 (32.8)	6 (10.7)	1 (5.6)	4 (18.2)	58 (20.6)
HCV/HIV co-infected, n (%)	4 (5.1)	1 (2.1)	0 (0)	6 (10.7)	0 (0)	0 (0)	11 (3.9)
Treatment history, n (%)							
Treatment-naive	67 (85.9)	45 (95.7)	52 (85.2)	42 (75.0)	14 (77.8)	17 (77.3)	237 (84.0)
Treatment-experienced	11 (14.1)	2 (4.3)	9 (14.8)	14 (25.0)	4 (22.2)	5 (22.7)	45 (16.0)
IL28B genotype, n (%)							
CC	23 (29.5)	23 (48.9)	24 (39.3)	17 (30.4)	1 (5.6)	16 (72.7)	104 (36.9)
Non-CC	53	24 (51.1)	35	39 (69.6)	17	6 (27.3)	174 (61.7)

	(67.9)		(57.4)		(94.4)		
Unknown	2 (2.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (1.4)

511 GT, genotype; HCV, hepatitis C virus; HIV, human immunodeficiency virus; SD, standard

512 deviation.

513

514

TABLE 2 SVR12 in the full analysis set population and the per protocol population.

	HCV genotype							All participants
	GT1a	**GT1b**	**GT2**	**GT3**	**GT4**	**GT5**	**GT6**	
Full analysis set	n=48	n=30	n=47	n=61	n=56	n=18	n=22	N=282
SVR, n/N (%)	43/48 (89.6%)	29/30 (96.7%)	43/47 (91.5%)	45/61 (73.8%)	55/56 (98.2%)	18/18 (100%)	20/22 (90.9%)	253/282 (89.7%)
Non-SVR, n	5	1	4	16	1	0	2	29
Relapse	3	0	1	14	0	0	1	19
Reinfection	0	0	0	1[a]	0	0	0	1
AE	1	0	0	1	1	0	0	3
DRAE	0	0	1	0	0	0	1	2
LTFU/withdrawn	1	1	2	0	0	0	0	4
Per-protocol analysis	n=45	n=29	n=44	n=59	n=55	n=18	n=22	N=272
Excluded from PP, n	3	1	3	2	1	0	0	10
SVR[b,c,d]	1[b]	0	1[c]	1[d]	0	0	0	3
Non-SVR	2	0	2	1	1	0	0	7
AE	1	0	0	1	1	0	0	3
LTFU/withdrawn	1	1	2	0	0	0	0	4
SVR, n/N (%)	42/45 (93.3%)	29/29 (100%)	42/44 (95.5%)	45/59 (76.3%)[a]	55/55 (100%)	18/18 (100%)	20/22 (90.9%)	251/272 (92.3%)
Non-SVR, n	3	0	2	14	0	0	2	21

Relapse	3	0	1	14	0	0	1	19
DRAE	0	0	1	0	0	0	1	2

AE, adverse event. DRAE, drug-related adverse event; GT, genotype; HCV, hepatitis C virus; LTFU, lost to follow-up; PP, per-protocol; SVR, sustained virologic response.

[a]One participant with HCV GT3 infection had evidence of reinfection during follow-up (GT3 at baseline, GT1a at follow-up week 8). This participant was considered as non-SVR within the full analysis set (FAS) analysis but was considered as achieving SVR within the PP analysis.

[b]One participant with HCV GT1a infection withdrew during treatment but continued in the study and had plasma collection 12 weeks after treatment discontinuation; this participant was considered as achieving SVR within the FAS analysis but was excluded from the PP analysis owing to withdrawal from study.

[c]One participant with HCV GT2 infection withdrew during treatment but continued in the study and had plasma collection 12 weeks after treatment discontinuation; this participant was considered as achieving SVR within the FAS analysis but was excluded from the PP analysis due to withdrawal from study.

[d]One participant with HCVGT3 infection withdrew during treatment but continued in the study and had plasma collection 12 weeks after treatment discontinuation; this participant was considered as achieving SVR within the FAS analysis but was excluded from the PP analysis owing to physician decision.

TABLE 3 SVR12 in select subgroups (per-protocol population).

HCV genotype		

	GT1a n=45	GT1b n=29	GT2 n=44	GT3 n=59	GT4 n=55	GT5 n=18	GT6 n=22	All participants N=272
Race, % (n/N)								
White	95.0 (38/40)	100.0 (26/26)	97.6 (40/41)	78.2 (43/55)	100.0 (46/46)	100.0 (4/4)	0	92.9 (197/212)
Black	50.0 (1/2)	100.0 (1/1)	0	0 (0/1)	100.0 (8/8)	100.0 (9/9)	0	90.5 (19/21)
Asian	0	100.0 (2/2)	100.0 (2/2)	50.0 (1/2)	0	100.0 (1/1)	90.9 (20/22)	89.7 (26/29)
Native Hawaiian or other Pacific Islander	100.0 (2/2)	0	0 (0/1)	0	100.0 (1/1)	0	0	75.0 (3/4)
Multiple	100.0 (1/1)	0	0	100.0 (1/1)	0	100.0 (4/4)	0	100.0 (6/6)
Cirrhosis status, % (n/N)								
Cirrhotic	88.9 (8/9)	100.0 (7/7)	100.0 (10/10)	68.4 (13/19)	100.0 (6/6)	100.0 (1/1)	100.0 (4/4)	87.5 (49/56)
Non-cirrhotic	97.1 (33/34)	100.0 (22/22)	94.1 (32/34)	80.0 (32/40)	100.0 (49/49)	100.0 (17/17)	88.9 (16/18)	93.5 (202/216)
Baseline HCV RNA, % (n/N)								

≤800,000 IU/mL	100.0 (10/10)	100.0 (7/7)	91.7 (11/12)	100.0 (15/15)	100.0 (16/16)	100.0 (4/4)	85.7 (6/7)	97.2 (70/72)
>800,000 IU/mL	91.4 (32/35)	100.0 (22/22)	96.9 (31/32)	68.2 (30/44)	100.0 (39/39)	100.0 (14/14)	93.3 (14/15)	90.5 (181/200)
≤2,000,000 IU/mL	100.0 (17/17)	100.0 (13/13)	94.1 (16/17)	91.3 (21/23)	100.0 (31/31)	100.0 (7/7)	88.9 (8/9)	96.6 (115/119)
>2,000,000 IU/mL	89.3 (25/28)	100.0 (16/16)	96.3 (26/27)	66.7 (24/36)	100.0 (24/24)	100.0 (11/11)	92.3 (12/13)	88.9 (136/153)

GT, genotype; HCV, hepatitis C virus.

FIGURE 1 Participant disposition by HCV genotype for SVR12.

AE, adverse event; GT, genotype; HCV, hepatitis C virus; LTFU, lost to follow-up; SVR12, sustained virologic response 12 weeks after end of treatment.

[a]Includes all participants who received at least one dose of study medication.

[b]Includes two individuals with HCV GT1-other infection.

FIGURE 2 SVR12 by HCV genotype and presence of baseline NS5A resistance-associated substitutions. Pie charts indicate prevalence of baseline RASs. NS5A substitutions at amino acid positions 28, 30, 31, and 93 were evaluated for all participants with HCV GT1-GT6 infection). In participants with GT3, GT4, GT5, and GT6 infection, NS5A substitutions at position 58 were also evaluated, and additionally, in participants with GT3 infection, substitutions at position 62 were evaluated.

GT, genotype; HCV, hepatitis C virus; NS5A, nonstructural protein 5 A; RAS, resistance-associated substitution; SVR12, sustained virologic response at 12 weeks after completion of therapy.

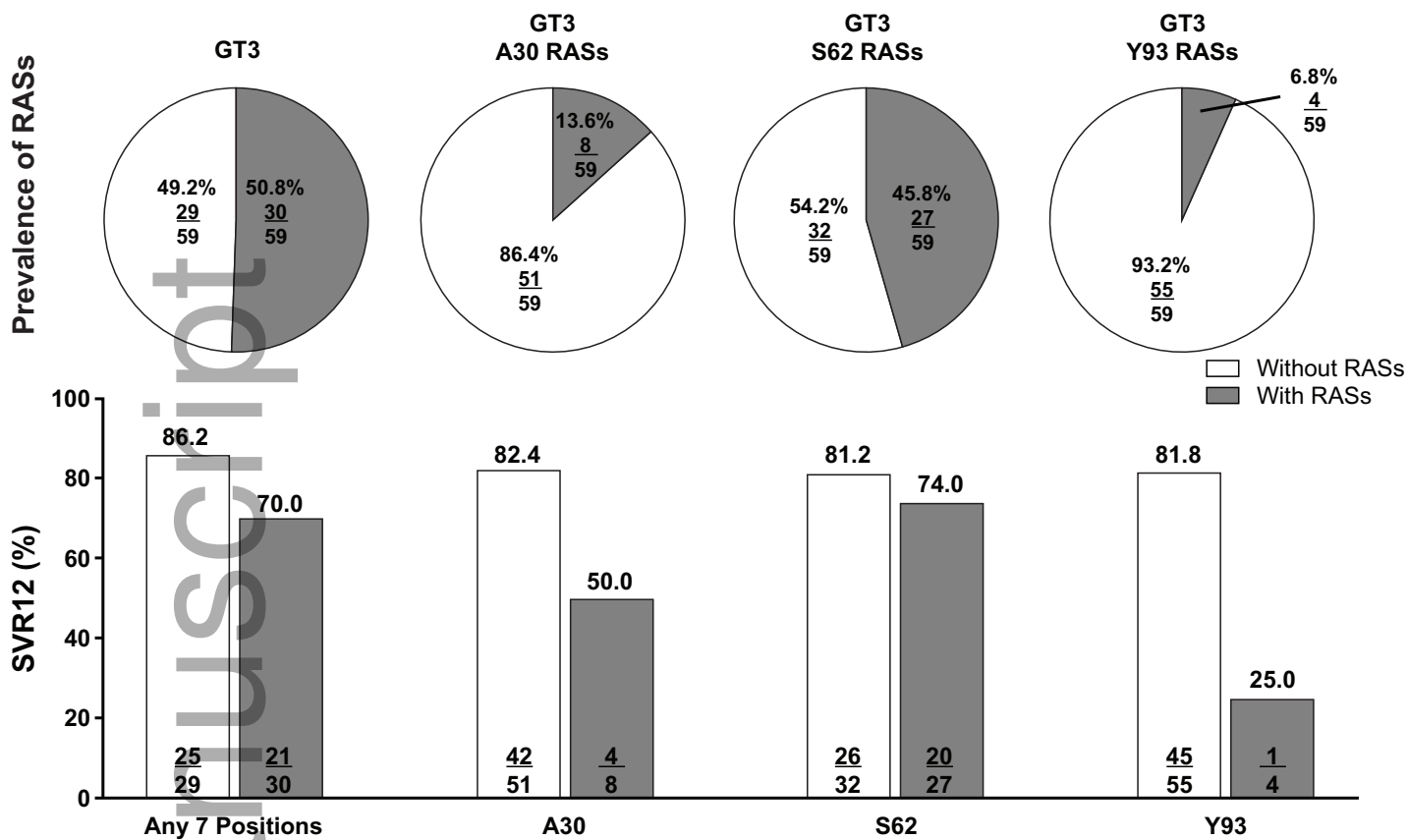[a]Includes two participants with HCV GT1-other infection.

FIGURE 3. SVR12 by HCV GT3 genotype and RAS. GT, genotype; HCV, hepatitis C virus; RAS, resistance-associated substitution; SVR12, sustained virologic response at 12 weeks after completion of therapy.
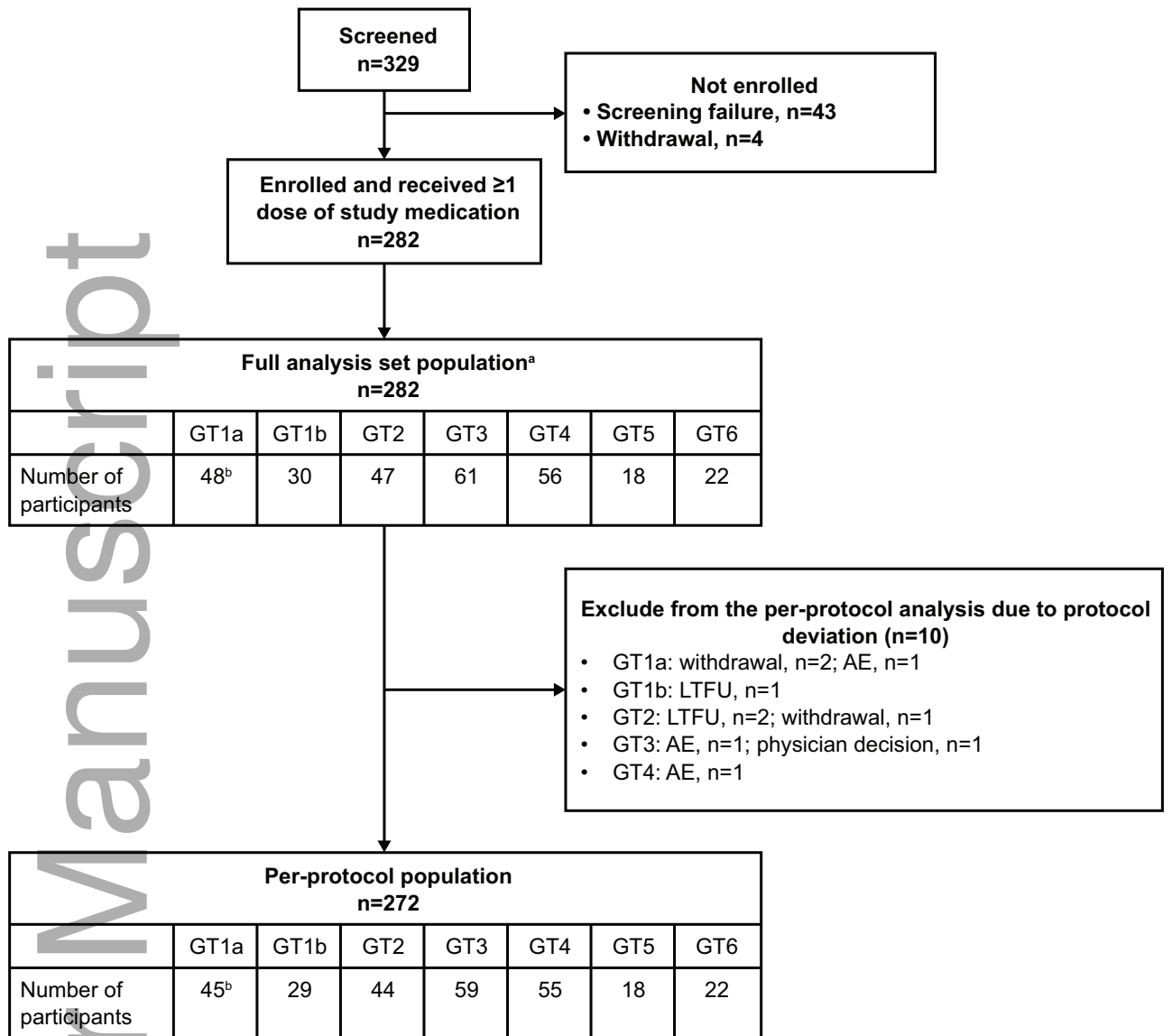
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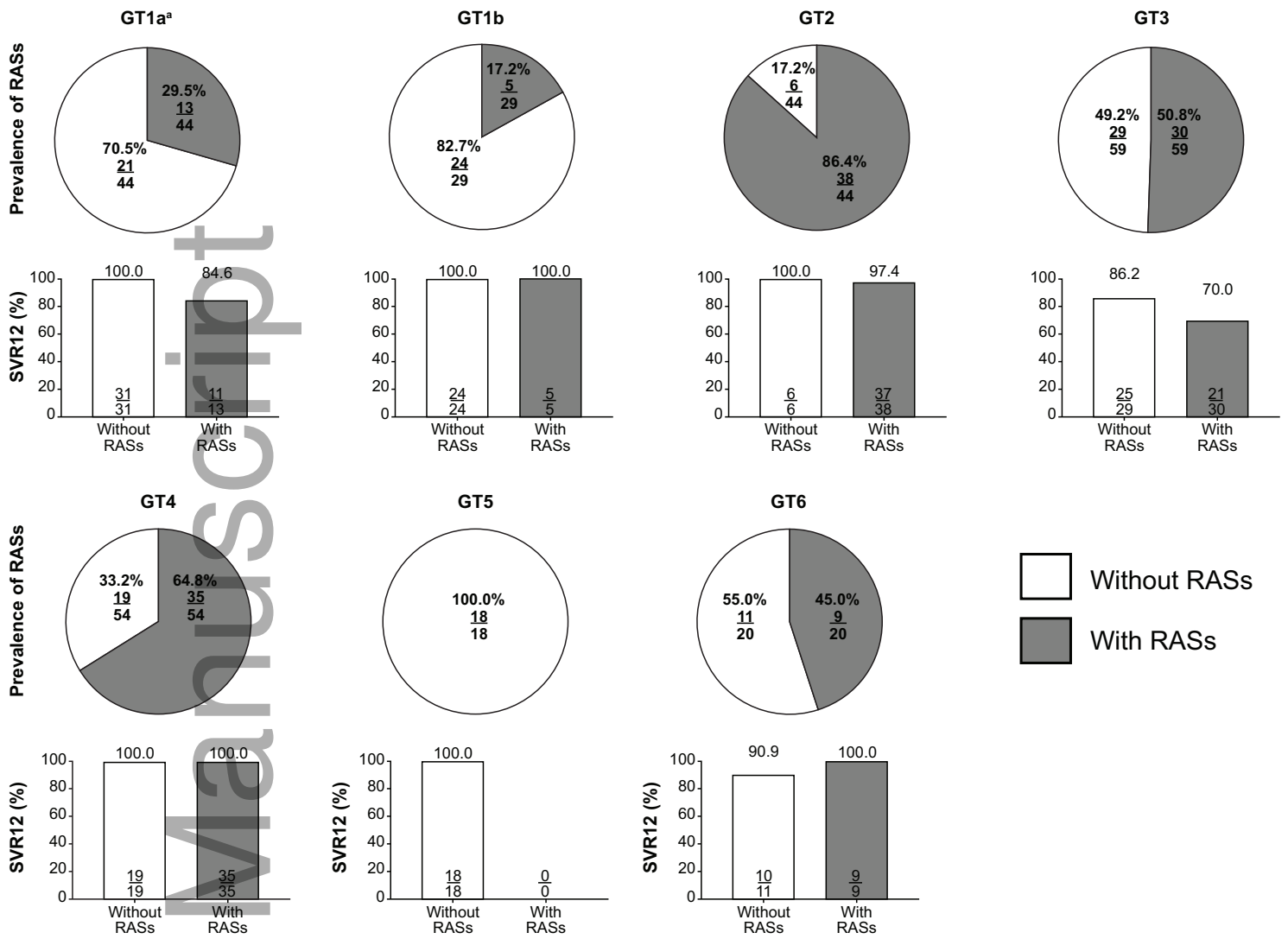
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Lawitz, E;Gane, E;Feld, JJ;Buti, M;Foster, GR;Rabinovitz, M;Burnevich, E;Katchman, H;Tomasiewicz, K;Lahser, F;Jackson, B;Shaughnessy, M;Klopfer, S;Yeh, WW;Robertson, MN;Hanna, GJ;Barr, E;Platt, HL;C-BREEZE-2 Study Investigators,

Title:
Efficacy and safety of a two-drug direct-acting antiviral agent regimen ruzasvir 180#mg and uprifosbuvir 450#mg for 12#weeks in adults with chronic hepatitis C virus genotype 1, 2, 3, 4, 5 or 6.

Date:
2019-09

Citation:
Lawitz, E., Gane, E., Feld, J. J., Buti, M., Foster, G. R., Rabinovitz, M., Burnevich, E., Katchman, H., Tomasiewicz, K., Lahser, F., Jackson, B., Shaughnessy, M., Klopfer, S., Yeh, W. W., Robertson, M. N., Hanna, G. J., Barr, E., Platt, H. L. & C-BREEZE-2 Study Investigators, (2019). Efficacy and safety of a two-drug direct-acting antiviral agent regimen ruzasvir 180#mg and uprifosbuvir 450#mg for 12#weeks in adults with chronic hepatitis C virus genotype 1, 2, 3, 4, 5 or 6.. J Viral Hepat, 26 (9), pp.1127-1138. https://doi.org/10.1111/jvh.13132.

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