

Appendix Table 2. Randomized, Controlled Trial of Participants Who Withdrew from Treatment and had AEs

AE	Studies, n	Treatment, n/n (%)	Control Participants, n/n (%)	Absolute Risk Difference (95% CI)	Relative Risk Ratio (95% CI)	Trial(s) Duration
Versus Placebo (63, 69)						
Participants not completing study/treatment	1	26/345 (7.5) (10 and 30 mg)	13/170 (7.6)	0 (-5 to 5)	0.99 (0.52 to 1.87)	48 wk
Any AE	1	94/123 (76.4)	45/61 (73.7)	3 (-11 to 16)	1.04 (0.87 to 1.24)	48 wk
Severe AE (grade III or IV)	2	24/294 (8.2)	19/228 (8.3)	0 (-6 to 6)	0.95 (0.45 to 2.01)	48 wk
AEs leading to discontinuation of study drug	2	4/294 (1.4)	1/228 (<1)	1 (-1 to 3)	2.34 (0.37 to 14.75)	48 wk
Versus lamivudine, participants with lamivudine resistance (72)						
Participants not completing study/treatment	1	1/20 (5)	1/19 (5.3)	0 (-14 to 14)	0.95 (0.06 to 14.13)	48 wk
Any AE	1	18/19 (94.7)	19/19 (100)	-5 (-19 to 8)	0.95 (0.82 to 1.09)	48 wk
Serious AE	1	3/19 (15.8)	1/19 (5.3)	11 (-9 to 30)	3.0 (0.34 to 26.3)	48 wk
AEs leading to discontinuation of study drug	1	0/19	0/19	0	–	48 wk
Versus telbivudine (74)						
Participants not completing study/treatment	1	2/45 (4.4)	2/45 (4.4)	0 (-9 to 9)	1.00 (0.13 to 7.43)	52 wk
Any AE	1	27/44 (61.4)	34/45 (75.6)	-14 (-33 to 5)	0.81 (0.61 to 1.08)	52 wk
AE leading to discontinuation of study drug	1	0/44	0/45	0	–	52 wk
B. Lamivudine monotherapy						
Versus Placebo (60, 67, 68)						
Participants not completing study/treatment	2	33/374 (8.8)	16/120 (13.3)	-1 (-7 to 4)	0.87 (0.51 to 1.49)	52-104 wk
Any AE	1	224/285 (78.6)	56/73 (76.7)	2 (-9 to 13)	1.02 (0.89 to 1.18)	52 wk
Serious AE	2	18/374 (4.8)	6/120 (5)	2 (-1 to 4)	1.24 (0.53 to 2.93)	52-104 wk
Versus placebo, participants refractory interferon therapy (80)						
Participants not completing study/treatment	1	9/119 (7.6)	10/56 (17.9)	-10 (-21 to 1)	0.42 (0.18 to 0.98)	68 wk
AE leading to discontinuation of study drug	1	1/119 (<1)	4/56 (7.1)	-6 (-13 to 1)	0.12 (0.01 to 1.03)	68 wk
Versus placebo, participants with advanced liver disease (41)						
Any AE	1	335/436 (76.8)	178/215 (82.8)	-6 (-12 to 0)	0.93 (0.86 to 1.01)	32 mo (median)

Serious AE	1	54/436 (12.4)	38/215 (17.7)	-5 (-11 to 1)	0.70 (0.48 to 1.03)	32 mo (median)
Versus Pegylated Interferon- α -2a monotherapy (49, 69)						
Participants not completing treatment/study	2	71/456 (15.6)	45/453 (9.9)	6 (1 to 10)	1.57 (1.10 to 2.22)	72 wk
Any AE	2	238/453 (52.5)	395/448 (88.2)	-36 (-43 to -29)	0.59 (0.51 to 0.69)	72 wk
Serious AE	2	10/453 (2.2)	21/448 (4.7)	-2 (-5 to 0)	0.47 (0.22 to 0.99)	72 wk
AE leading to discontinuation of study drug	2	2/453 (<1)	21/448 (4.7)	-5 (-10 to 1)	0.13 (0.20 to 0.90)	72 wk
Dose modification due to AE	2	0/453	33/448 (7.4)	-7 (-10 to -5)	0.03 (0.00 to 0.22)	72 wk

C. Telbivudine monotherapy

Versus Adefovir (see above)

Versus lamivudine, attributed to study drug (SEBIVO INSERT – 007 GLOBE) (77)

Participants not completing treatment/study	1	18/680 (2.6)	32/687 (4.7)	-2 (-4 to 0)	0.57 (0.32 to 1.00)	52 wk
Any AE	–	NR	NR	–	–	52 wk
Serious AE	1	18/680 (2.6)	33/687 (4.8)	-2 (-4 to 0)	0.55 (0.31 to 0.97)	52 wk
AE leading to discontinuation of study drug	1	2/680 (<1)	5/687 (<1)	0 (-1 to 0)	0.40 (0.08 to 2.08)	52 wk
AE leading to discontinuation, possibly related to study drug	1	1/680 myopathy	1/687 urticaria	0 (0 to 0)	1.01 (0.06 to 16.12)	52 wk

D. Entecavir monotherapy (acyclic guanosine derivative)

0.5-mg dose vs. lamivudine, nucleoside-naive participants (44, 45)

Participants not completing study/treatment	2	37/688 (5.4)	58/675 (8.6)	-3 (-8 to 2)	0.64 (0.33 to 1.26)	Entecavir 56-75 wk lamivudin e56-65 wk
Any AE	2	552/679 (80.3)	545/668 (81.1)	0 (-6 to 6)	1.00 (0.92 to 1.08)	Entecavir 56-75 wk lamivudin e 56-65 wk
Serious AE	2	48/679 (7.1)	54/668 (8.1)	-1 (-4 to 2)	0.88 (0.60 to 1.27)	Entecavir 56-75 wk lamivudin e56-65 wk
AE leading to discontinuation of study drug	2	7/679 (1.0)	18/668 (2.7)	-2 (-3 to 0)	0.33 (0.06 to 1.86)	Entecavir 56-75 wk lamivudin e56-65 wk
0.5-mg dose vs. lamivudine, nucleoside-naive participants (patient information sheet [Bristol Myers Squibb])†						
Any Grade 2-4 AE	1	102/679 (15)	120/668 (18)	-3 (-7 to 1)	0.84 (0.66 to 1.06)	Through 2 y

1-mg dose vs. lamivudine in lamivudine-refractory participants (patient information sheet [Bristol Myers Squibb])†

Any Grade 2-4 AE	2	40/183 (21.9)	44/190 (23.2)	-1 (-10 to 7)	0.94 (0.87 to 1.14)	Through 2 y
Versus lamivudine in lamivudine-refractory participants (43, 46)						
Participants not completing study/treatment (48 wks)	2	39/283 (13.9)	38/191 (19.9)	-12 (-30 to 6)	0.54 (0.36 to 0.81)	48 wk
AE leading to discontinuation of study drug	2	11/277 (4.0)	14/190 (7.4)	-5 (-9 to 1)	0.43 (0.12 to 1.54)	48 wk
Any AE	2	225/277 (81.2)	155/190 (81.6)	0 (-12 to 11)	0.99 (0.87 to 1.14)	48 wk
Serious AE	2	22/277 (7.9)	14/190 (7.4)	1 (-4 to 6)	1.18 (0.62 to 2.27)	48 wk

E. Pegylated interferon- α 2a monotherapy (see lamivudine section)

F. Combination pegylated interferon- α 2a and lamivudine therapy

Versus lamivudine (see above) (49, 69)

Versus pegylated interferon- α 2a monotherapy (49, 69)

Participants not completing treatment/study	2	49/457 (10.7)	45/453 (9.9)	1 (-4 to 5)	1.08 (0.71 to 1.66)	72 wk
Any AE	2	395/450 (87.8)	395/448 (88.2)	0 (-58 to 4)	1.00 (0.95 to 1.05)	72 wk
Serious AE	2	28/450 (6.2)	21/448 (4.7)	2 (-1 to 4)	1.33 (0.77 to 2.30)	72 wk
AE leading to discontinuation of study drug	2	19/450 (4.2)	21/448 (4.7)	-1 (-6 to 4)	0.90 (0.33 to 2.48)	72 wk

G. Combination Pegylated interferon- α -2b and Lamivudine therapy (Interferon)

Versus pegylated interferon- α 2b monotherapy (90)

Participants not completing treatment/study	1	38/152 (25)	37/155 (23.9)	1 (-8 to 11)	1.05 (0.71 to 1.55)	78 wk
Serious AE	1	32 total, 17 probably related to therapy.				78 wk
AE leading to discontinuation of study drug	1	12/152 (7.9)	11/155 (7.1)	1 (-5 to 7)	1.11 (0.51 to 2.44)	78 wk

I. Pegylated interferon- α 2b versus interferon- α 2b (93)

Participants not completing treatment/study	1	7/115 (6.1)	20/115 (17.4)	-11 (-19 to -3)	0.35 (0.15 to 0.80)	72 wk
AE leading to discontinuation of study drug	1	0/115	4/115 (3.5)	-3 (-7 to 0)	0.11 (0.01 to 2.04)	72 wk
Any AE	75% of patients in each treatment group experienced various clinical forms of drug-related adverse effects.					72 wk

K. Interferon- α -2b monotherapy (interferon)

Prolonged (32 wk) versus standard (16 wk) duration (35)

Dose reduction due to AE: 11.5% (7/61) in the prolonged group; not reported in standard group.

AE leading to discontinuation of study drug: 4.9% (3/61) in the prolonged group; not reported in standard group.

Phase A: all participants before randomly assigned: dose modification due to AE: 16/162 (10%).

Versus no treatment (reference)

(36) 6 mo ($n = 19$) vs. 12 mo ($n = 19$). Treatment was well tolerated by all participants who finished the study, and no dose modification was needed.

(40) IFN ($n = 20$) vs. no treatment ($n = 20$). Study duration was 68 wks. 4 IFN and 5 NT participants did not complete study.

(55) IFN ($n = 30$) vs. no treatment ($n = 28$). Study duration was 10 mo. One participant with a preexisting depressive state converted to overt depression and was taken off treatment.

(32) IFN ($n = 25$) vs. no treatment ($n = 25$). Study duration was 52 wks. IFN therapy well tolerated. No serious AE observed.

AE = adverse events; ALT = alanine aminotransferase; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis virus B; IFN = interferon therapy; MU = million units; NT = no treatment; NS = statistically nonsignificant; RCT = randomized, controlled trial; RD = risk difference; RR = relative risk;

* Statistically significant at 95% level

† New York, New York.