Supplementary Appendix

Table of Contents

I. List of Investigators

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II. Supplementary Methods: Study Objectives

As previously discussed,(1) this study was designed to adequately assess the efficacy of cenicriviroc (CVC) treatment for fibrotic nonalcoholic steatohepatitis (NASH), based on previous phase 2 studies as well as contemporary phase 3 studies.

Since the time of protocol writing and study initiation but prior to database lock for the year 1 primary analysis, the definitions of the primary and key secondary efficacy end points were adapted to reflect the most recent recommendations from regulatory authorities at open forums and separately with the sponsor in the study's statistical analysis plan.(2) Consequently, the protocol and statistical analysis plan were amended (detailed below) to reflect the update in the definitions.

Please note that the CENTAUR study uses the same definitions for the resolution of NASH as in the PIVENS and FLINT studies, which are based on the definitions from Brunt and Kleiner.(3, 4)

III. Supplementary Figures

Figure S1. CENTAUR Study Efficacy End Points.*

Primary Efficacy End Point	Key Secondary Efficacy End Points
• Hepatic histological improvement in NAS relative to screening biopsy (≥2-point improvement in NAS with ≥1-point reduction in either lobular inflammation or hepatocellular ballooning) and no worsening of fibrosis† at **year 1**	• Complete resolution of NASH‡ and no worsening of fibrosis† at **year 1** • Improvement in fibrosis by ≥1 stage (NASH CRN system) and no worsening of steatohepatitis§ at **year 1**

Other Secondary Efficacy End Points
• Complete resolution of NASH‡ and no worsening of fibrosis at **year 2**
• Improvement in fibrosis by at least 1 stage (NASH CRN system) and no worsening of steatohepatitis§ at **year 2**
• Hepatic histological improvement in NAS at year 2 relative to screening biopsy (≥2-point drop in NAS with ≥1-point reduction in either lobular inflammation or hepatocellular ballooning) and no worsening of fibrosis at **year 2**
• Changes in each of the categorical features of NAS (steatosis, lobular inflammation, hepatocellular ballooning) at **years 1 and 2**
• Hepatic histological improvement in NAS relative to the screening biopsy using a modified definition of ≥2-point improvement in NAS with ≥1-point improvement in more than 1 category (steatosis, lobular inflammation, and hepatocellular ballooning) and no worsening of fibrosis stage† at **years 1 and 2**
• Resolution of NASH using a modified definition based on categorical features of NAS and defined as having no hepatocellular ballooning (grade 0) and minimal to no lobular inflammation (grade 1 or 0) and no worsening of fibrosis stage (worsening defined as progression of NASH CRN fibrosis stage) at **years 1 and 2**
• Change in morphometric quantitative collagen on liver biopsy at **years 1 and 2**
• Change in hepatic tissue fibrogenic protein (α-SMA) at **years 1 and 2**
• Change in morphometric fat content on liver biopsy at **years 1 and 2**
• Change in histologic fibrosis stage (NASH CRN and Ishak systems) at **years 1 and 2**
• Change in portal inflammation grade on liver biopsy at **years 1 and 2**
• Change from baseline in noninvasive markers of hepatic fibrosis (APRI, FIB-4, hyaluronic acid, FibroTest [FibroSure], NFS, and ELF at **months 3, 6, 12, 15, 18, and 24**
• Change from baseline in biomarkers of hepatocyte apoptosis (CK-18 caspase-cleaved [M30] and total [M65]) at **months 3, 6, 12, 15, 18 and 24**
• Change from baseline in liver parameters and fasting metabolic parameters **at months 3, 6, 12, 15, 18, and 24**
• Change from baseline in weight, BMI, waist circumference, waist–hip ratio, arm circumference, and tricep skinfold **at months 3, 6, 12, 15, 18, and 24**

Tertiary Efficacy End Points
Change from baseline in noninvasive liver imaging method (e.g. UTE, 2D-MRE, and ARFI) at months 6, 12, 18, and 24 (at sites where available)

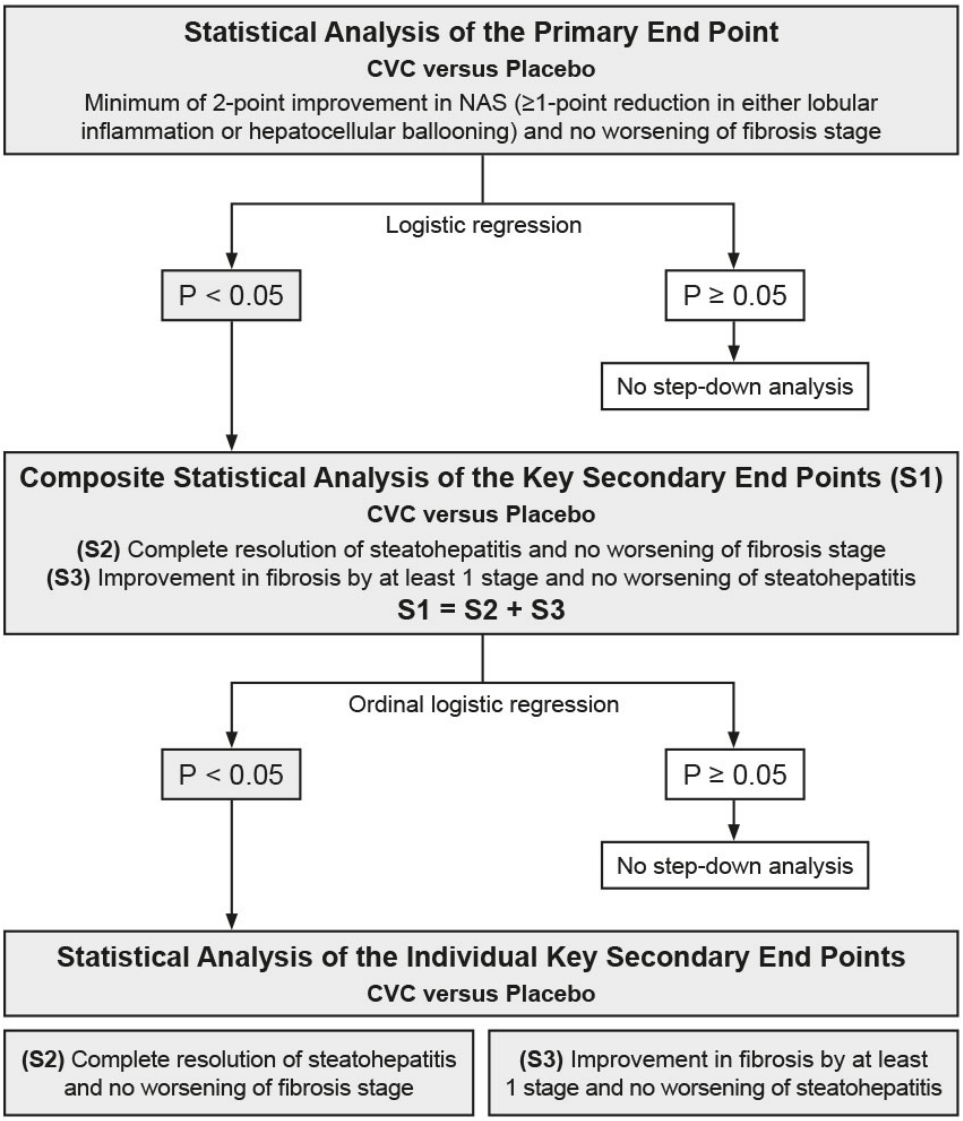
*α-SMA denotes α-smooth muscle actin, APRI aspartate aminotransferase-to-platelet ratio index, ARFI acoustic radiation force impulse, BMI body mass index, CK-18 cytokeratin 18, CRN Clinical Research Network, ELF enhanced liver fibrosis, FIB-4 fibrosis-4, 2D-MRE 2-dimensional magnetic resonance elastography, NAS nonalcoholic fatty liver disease activity score, NASH nonalcoholic steatohepatitis, NFS nonalcoholic fatty liver disease fibrosis score, and UTE ultrasound transient elastography.

†Worsening defined as progression of NASH CRN fibrosis stage.

‡Histopathologic interpretation of no fatty liver disease or simple or isolated steatosis and no steatohepatitis.

§No worsening of lobular inflammation or hepatocellular ballooning grade.

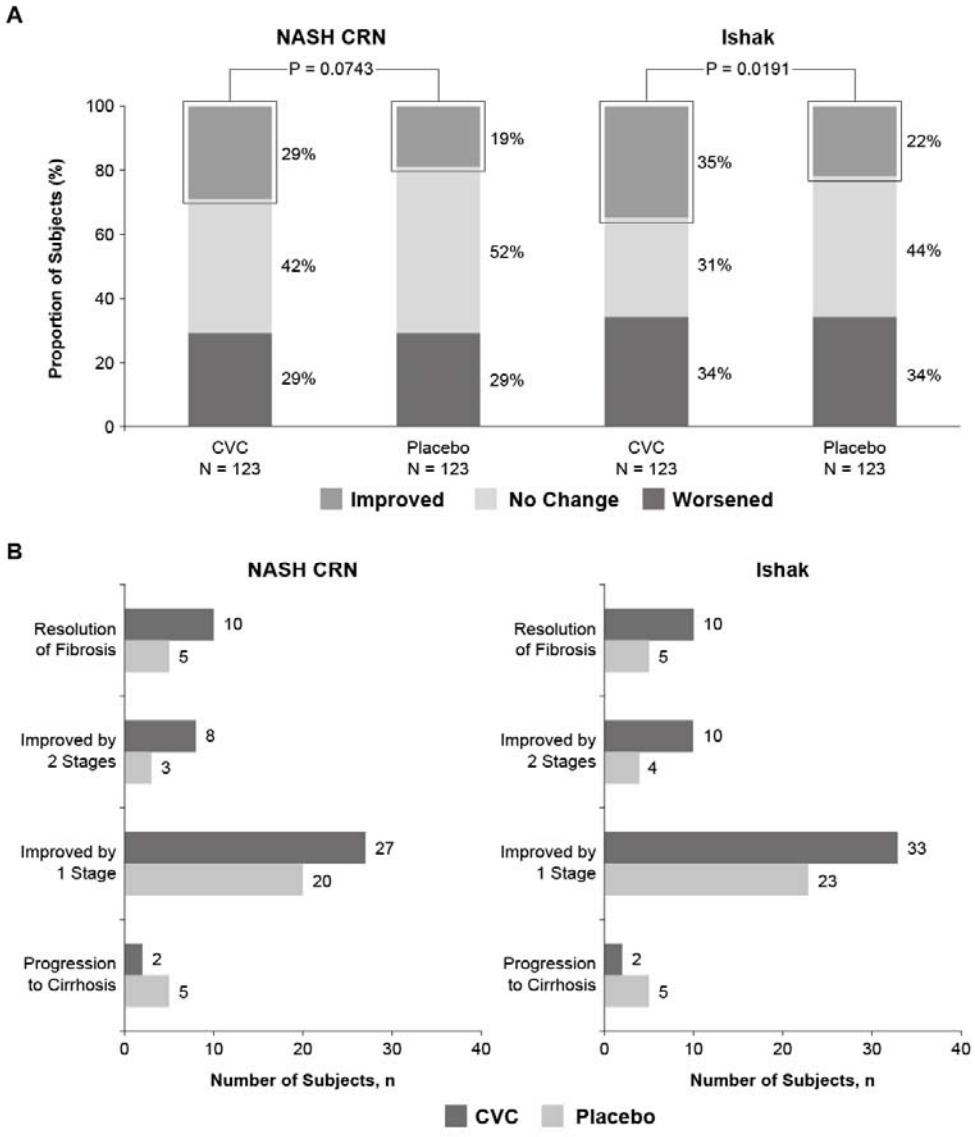
Figure S2. Planned Step-Down Approach Used for the Statistical Analysis of the CENTAUR Study Efficacy End Points.*



*CVC denotes cenicriviroc, and NAS nonalcoholic fatty liver disease activity score.

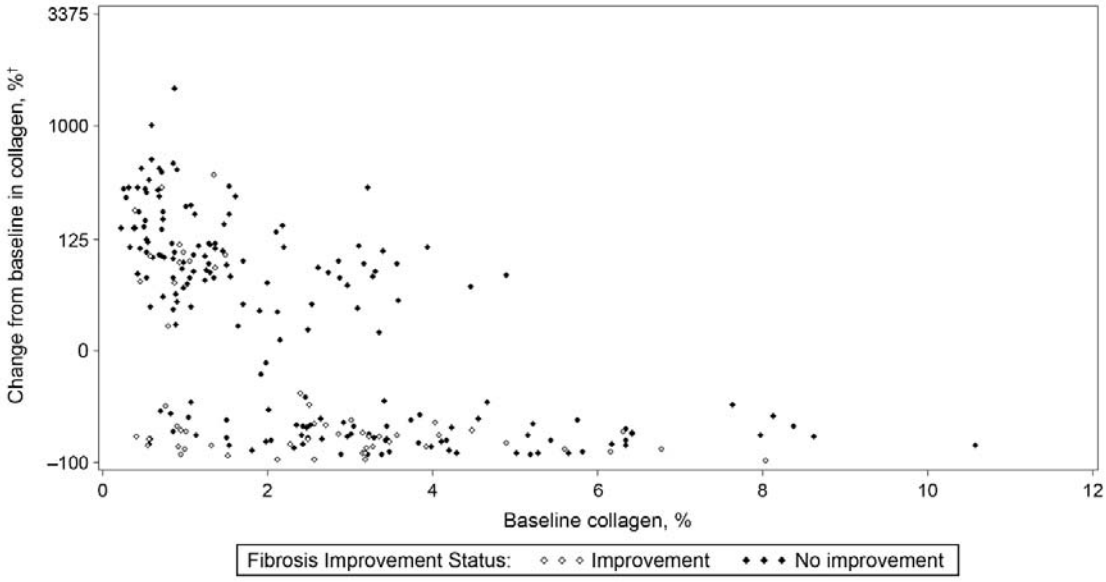
Figure S3. Changes in Fibrosis Stage (NASH CRN and Ishak Systems) (PP Population).*

Panel A shows the proportion of subjects who improved, had no change in, or had worsening of fibrosis stage at year 1. Panel B shows the number of subjects with changes in the NASH CRN or Ishak fibrosis system at year 1.



*CVC denotes cenicriviroc, NASH CRN nonalcoholic steatohepatitis Clinical Research Network, and PP per protocol.

Figure S4. Change from Baseline to Year 1 *versus* Baseline Morphometric Quantitative Collagen, by NASH CRN Fibrosis Improvement Status at Year 1 (mITT Population).*



*mITT denotes modified intent-to-treat, and NASH CRN nonalcoholic steatohepatitis Clinical Research Network.

†Vertical axis presented with cube root spacing.

IV. Supplementary Tables

Table S1. Use of concomitant medications during CENTAUR Study Year 1

	HMG CoA reductase inhibitors	Biguanides	Angiotensin II inhibitors	Glucose lowering drugs excluding insulin
Used at any time during year 1				
CVC, %	35.4	52.8	22.9	16.7
Placebo, %	37.5	46.5	18.1	9.7
New or changed during year 1				
CVC, %	11.8	9.7	5.6	9.0
Placebo, %	9.0	14.6	2.8	6.3

CVC, cenicriviroc; HMG CoA, hydroxymethylglutaryl CoA

Table S2. CENTAUR Study Objectives and Procedures.*

Subjects were randomized 2:1:1 to arm A (CVC 150 mg once daily for 2 years), arm B (placebo for 1 year then CVC 150 mg for 1 year), or arm C (placebo for 2 years).

	Study Time Point — Months					
Study Objectives (Year 1: Arm A vs. arms B and C; year 2: arm A vs. arm C)	**3**	**6**	**12**	**15**	**18**	**24**
Primary objective						
Evaluate hepatic histological improvement in NAS relative to screening biopsy (≥2-point improvement in NAS with at least a 1-point reduction in either lobular inflammation or hepatocellular ballooning) and no worsening of fibrosis† at **year 1**			X			
Key secondary objectives						
• Evaluate the complete resolution of NASH‡ and no worsening of fibrosis† at **year 1**			X			
• Evaluate the improvement in fibrosis by at least 1 stage (NASH CRN system) and no worsening of steatohepatitis§ at **year 1**			X			
Other secondary objectives						
• Evaluate the complete resolution of NASH‡ and no worsening of fibrosis† at **year 2**						X
• Evaluate the improvement in fibrosis by at least 1 stage (NASH CRN system) and no worsening of steatohepatitis§ at **year 2**						X
• Assessment of CVC safety and tolerability over **years 1 and 2**	Continuous					
• Plasma PK of CVC in a population PK analysis¶	X	X	X	X	X	X

• Evaluate hepatic histological improvement in NAS relative to screening biopsy (2-point improvement in NAS with at least a 1-point reduction in either lobular inflammation or hepatocellular ballooning) and no worsening of fibrosis† at **year 2**						X
• Evaluate changes in each of the categorical features of NAS (steatosis, lobular inflammation, hepatocellular ballooning) at **years 1 and 2**			X			X
• Evaluate hepatic histological improvement in NAS relative to the screening biopsy (modified definition of 2-point improvement in NAS with at least a 1-point improvement in more than 1 category [steatosis, lobular inflammation, and hepatocellular ballooning]) and no worsening of fibrosis stage† at **years 1 and 2**			X			X
• Evaluate resolution of NASH using a modified definition based on categorical features of NAS and defined as having no hepatocellular ballooning (grade 0) and minimal to no lobular inflammation (grade 1 or 0), and no worsening of fibrosis stage (worsening defined as progression of NASH CRN fibrosis stage) at **years 1 and 2**			X			X
• Evaluate the efficacy of CVC versus placebo in adult subjects with liver fibrosis as determined by change in morphometric quantitative collagen on liver biopsy at **years 1 and 2**			X			X
• Evaluate the change in histological fibrosis stage assessed using NASH CRN and Ishak systems at **years 1 and 2**			X			X
• Evaluate the change in hepatic stellate cell activation marker (α-SMA) at **years 1 and 2**			X			X

• Evaluate the change in morphometric quantitative fat content on liver biopsy at **years 1 and 2**			X			X
• Evaluate the change in portal inflammation grade on liver biopsy at **years 1 and 2**			X			X
• Evaluate change from baseline in noninvasive scores and markers of hepatic fibrosis (APRI, FIB-4, hyaluronic acid, FibroTest [FibroSure], NFS, and ELF)	X	X	X	X	X	X
• Evaluate the change from baseline in biomarkers of hepatocyte apoptosis, assessed using CK-18 caspase-cleaved and total	X	X	X	X	X	X
• Evaluate the change from baseline in liver biochemistry and fasting metabolite parameters	X	X	X	X	X	X
• Change from baseline in weight, BMI, waist circumference, waist–hip ratio, arm circumference, and tricep skinfold	X	X	X	X	X	X
Tertiary objectives						
• Evaluate the change from baseline by noninvasive liver imaging method (e.g., UTE, 2D-MRE, and ARFI)‖		X	X		X	X
• Change from baseline in pro-inflammatory cytokines and biomarkers of inflammation	X	X	X	X	X	X
• Change from baseline in eGFR	X	X	X	X	X	X
• Change from baseline in biomarkers associated with bacterial translocation	X	X	X	X	X	X

*α-SMA denotes α-smooth muscle actin, APRI aspartate aminotransferase-to-platelet ratio index, ARFI acoustic radiation force impulse, BMI body mass index, CK-18, cytokeratin 18; CRN Clinical Research Network, CVC cenicriviroc, eGFR estimated glomerular filtration rate, ELF enhanced liver fibrosis, FIB-4 fibrosis-4, 2D-MRE 2-dimensional magnetic resonance elastography, NAS nonalcoholic

fatty liver disease activity score, NASH nonalcoholic steatohepatitis, NFS nonalcoholic fatty liver disease fibrosis score, PK pharmacokinetics, and UTE ultrasound transient elastography.

†Worsening defined as progression of NASH CRN fibrosis stage.

‡Histopathologic interpretation of no fatty liver disease, or simple or isolated steatosis and no steatohepatitis.

§No worsening of lobular inflammation or hepatocellular ballooning grade.

¶Plasma samples for population PK analysis will be collected on day 1 (baseline) and months 0.5, 3, 6, 12, 15, 18, and 24.

‖At sites where available.

Table S3. Analysis of the Key Secondary Efficacy End Point, Improvement in Fibrosis by at Least One Stage and No Worsening of Steatohepatitis, by Liver Biopsy Length (mITT population).*

Baseline biopsy length **End point response, n (%)**	**CVC 150 mg** **(N = 126)**	**Placebo** **(N = 144)**	**OR and** **95% CI** **(CVC/Placebo)**	***P* value**
Baseline biopsy length **<15 mm**	N = 28	N = 22	3.999 (0.754, 21.219)	0.1035
1 = Yes	8 (28.6)	2 (9.1)		
0 = No	20 (71.4)	20 (90.9)		
Baseline biopsy length **≥15 mm**	N = 98	N = 104	1.909 (0.897, 4.063)	0.0934
1 = Yes	21 (21.4)	13 (12.5)		
0 = No	77 (78.6)	91 (87.5)		
Year 1 biopsy length **<15 mm**	N = 23	N = 27	0.737 (0.180, 3.016)	0.6710
1 = Yes	4 (17.4)	6 (22.2)		
0 = No	19 (82.6)	21 (77.8)		
Year 1 biopsy length **≥15 mm**	N = 103	N = 99	3.205 (1.412, 7.277)	0.0054
1 = Yes	25 (24.3)	9 (9.1)		
0 = No	78 (75.7)	90 (90.9)		

*CI denotes confidence interval, CVC cenicriviroc, mITT modified intent-to-treat, and OR odds ratio.

Table S4. Change from Baseline in Liver Biopsy Steatosis, Lobular Inflammation, and Hepatocellular Ballooning at Year 1 (PP Population).*

	CVC 150 mg (N = 123)†			Placebo (N = 123)†		
	Improved	No change	Worsened	Improved	No change	Worsened
Steatosis‡						
no.	24	91	8	31	76	16
%	**19.5**	**74.0**	**6.5**	**25.2**	**61.8**	**13.0**
Lobular inflammation§						
no.	39	54	30	34	61	28
%	**31.7**	**43.9**	**24.4**	**27.6**	**49.6**	**22.8**
Hepatocellular ballooning¶						
no.	33	67	23	43	62	18
%	**26.8**	**54.5**	**18.7**	**35.0**	**50.4**	**14.6**

*CVC denotes cenicriviroc, and PP per-protocol.

†Subjects without evaluable biopsy results at both baseline and year 1 are excluded.

‡Grade defined as 0=<5%, 1=5%–33%, 2=>33%–66%, 3=>66%.

§Grade defined as 0=no foci, 1=<2 foci/200x, 2=2–4 foci/200x, 3=>4 foci/200x.

¶Grade defined as 0=none, 1=few balloon cells, 2=many cells/prominent ballooning.

Table S5. Change from Baseline to Liver Biochemistry and Fasting Metabolic Parameters at Year 1 (Safety Population).*

	CVC 150 mg (N = 144)			Placebo (N = 144)		
	Baseline	Year 1	Change	Baseline	Year 1	Change
ALP						
no.	123	123	123	124	124	124
Mean (SD), U/L	78.25 (20.95)	79.22 (23.27)	0.97 (15.57)	81.44 (29.02)	96.96 (121.03)	15.52 (116.81)
ALT						
no.	123	123	123	124	124	124
Mean (SD), U/L	60.37 (34.32)	67.15 (46.68)	6.78 (37.28)	64.12 (36.09)	64.87 (55.03)	0.75 (49.69)
Albumin						
no.	123	123	123	124	124	124
Mean (SD), g/L	44.33 (3.74)	43.59 (3.89)	–0.74 (3.01)	44.40 (3.98)	43.71 (3.78)	–0.69 (2.59)
AST						
no.	122	122	122	123	123	123
Mean (SD), U/L	43.29 (22.39)	48.34 (31.26)	5.05 (27.91)	48.06 (23.07)	50.85 (41.34)	2.80 (39.65)

Direct bilirubin						
no.	122	122	122	123	123	123
Mean (SD), µmol/L	2.64 (1.91)	2.76 (1.87)	0.12 (0.93)	2.73 (1.55)	3.15 (4.65)	0.42 (4.27)
Total bilirubin						
no.	123	123	123	124	124	124
Mean (SD), µmol/L	9.02 (9.69)	8.94 (7.20)	–0.09 (5.33)	8.46 (4.80)	8.53 (6.79)	0.07 (5.72)
GGT						
no.	123	123	123	124	124	124
Mean (SD), U/L	68.94 (81.76)	70.79 (94.93)	1.85 (34.75)	66.03 (44.45)	80.99 (190.51)	14.96 (190.21)
Total cholesterol						
no.	123	123	123	124	124	124
Mean (SD), mmol/L	4.95 (1.12)	4.93 (1.19)	–0.03 (0.83)	4.80 (1.24)	4.85 (1.15)	0.04 (0.93)
HDL cholesterol						
no.	120	120	120	123	123	123
Mean (SD), mmol/L	1.08 (0.34)	1.08 (0.34)	–0.01 (0.20)	1.06 (0.36)	1.08 (0.35)	0.02 (0.23)
LDL cholesterol						

no.	119	119	119	123	123	123
Mean (SD), mmol/L	3.13 (0.95)	3.13 (1.02)	0.01 (0.70)	3.03 (1.12)	2.97 (1.00)	–0.07 (0.74)
VLDL cholesterol						
no.	120	120	120	124	124	124
Mean (SD), mmol/L	0.96 (0.83)	0.91 (0.63)	–0.06 (0.76)	0.90 (0.58)	1.00 (0.94)	0.10 (0.73)
Triglycerides						
no.	123	123	123	124	124	124
Mean (SD), mmol/L	2.08 (1.79)	1.98 (1.37)	–0.10 (1.67)	1.95 (1.27)	2.17 (2.05)	0.22 (1.59)
Fasting glucose						
no.	116	116	116	115	115	115
Mean (SD), mmol/L	6.93 (2.23)	6.96 (2.38)	0.03 (1.89)	6.48 (2.09)	6.82 (2.05)	0.34 (2.05)
Insulin						
no.	119	119	119	120	120	120
Mean (SD), mIU/L	27.07 (21.15)	27.65 (22.64)	0.59 (26.49)	29.35 (25.85)	33.18 (34.33)	3.82 (26.85)
HOMA-IR						
no.	110	110	110	110	110	110

Mean (SD)	8.46 (8.21)	8.00 (5.79)	–0.46 (8.73)	9.56 (13.21)	10.54 (12.79)	0.98 (13.37)
Non-esterified fatty acid						
no.	114	114	114	118	118	118
Mean (SD), mmol/L	0.58 (0.23)	0.57 (0.25)	–0.01 (0.26)	0.61 (0.24)	0.56 (0.23)	–0.05 (0.27)
Adipose tissue insulin resistance						
no.	113	113	113	118	118	118
Mean (SD)	14.04 (8.44)	14.37 (9.72)	0.33 (10.33)	16.33 (12.78)	16.78 (14.22)	0.45 (14.01)
HbA1c						
no.	121	121	121	122	122	122
Mean (SD), %	6.71 (1.35)	6.66 (1.42)	–0.05 (0.87)	6.37 (1.10)	6.45 (1.16)	0.08 (0.78)
Adiponectin						
no.	119	119	119	121	121	121
Mean (SD), µg/mL	4.83 (2.85)	4.25 (2.87)	–0.59 (1.58)	4.36 (2.90)	4.03 (2.61)	–0.33 (1.42)
Resistin						
no.	122	122	122	121	121	121

Mean (SD), µg/L	11.63	10.08	–1.55	11.22	10.58	–0.64
	(5.62)	(5.00)	(3.46)	(5.70)	(5.01)	(2.53)

*ALP denotes alkaline phosphatase, ALT alanine aminotransferase, AST aspartate aminotransferase, CVC cenicriviroc, GGT gamma-glutamyl transferase, HbA1c hemoglobin A1c, HDL high-density lipoprotein, HOMA-IR homeostatic model assessment of insulin resistance, LDL low-density lipoprotein, SD standard deviation, VLDL very-low-density lipoprotein.

Table S6. Change from Baseline to Year 1 in Liver Fibrosis Indices in All Subjects (PP population) and by NASH CRN Fibrosis Improvement Status at Year 1 (mITT population).*

	CVC 150 mg (N = 144)			Placebo (N = 143)		
	Baseline	Year 1	Change	Baseline	Year 1	Change
NFS						
All subjects						
no.	107	107	107	109	109	109
Median (min, max)	–0.942 (–4.55, 1.27)	–0.783 (–4.19, 2.25)	0.153 (–1.35, 1.43)	–1.223 (–4.81, 2.46)	–1.190 (–4.27, 2.34)	0.102 (–1.74, 1.37)
95% CI for difference in change from baseline (CVC 150 mg – placebo)			(–0.10, 0.17)			
Subjects with improvement						
no.	31	31	31	22	22	22
Mean (SD)	–1.28 (1.24)	–1.24 (1.21)	0.05 (0.52)	–1.26 (1.46)	–1.24 (1.61)	0.02 (0.64)

95% CI for difference in change from baseline (CVC 150 mg – placebo)			(–0.29, 0.35)			
Subjects without improvement						
no.	76	76	76	90	90	90
Mean (SD)	–0.99 (1.09)	–0.80 (1.21)	0.19 (0.49)	–1.13 (1.48)	–0.99 (1.41)	0.15 (0.48)
95% CI for difference in change from baseline (CVC 150 mg – placebo)			(–0.10, 0.19)			
FIB-4						
All subjects						
no.	114	114	114	112	112	112
Median (min, max)	1.239 (0.38, 4.20)	1.375 (0.42, 5.26)	0.080 (–1.81, 2.38)	1.303 (0.40, 4.14)	1.242 (0.36, 5.32)	0.006 (–1.18, 3.11)

95% CI for difference in change from baseline (CVC 150 mg – placebo)			(–0.12, 0.19)			
Subjects with improvement						
no.	31	31	31	23	23	23
Mean (SD)	1.27 (0.59)	1.29 (0.63)	0.02 (0.41)	1.31 (0.63)	1.17 (0.60)	–0.14 (0.49)
95% CI for difference in change from baseline (CVC 150 mg – placebo)			(–0.09, 0.41)			
Subjects without improvement						
no.	83	83	83	92	92	92
Mean (SD)	1.44 (0.72)	1.61 (0.82)	0.16 (0.54)	1.55 (0.76)	1.72 (1.05)	0.17 (0.73)

95% CI for difference in change from baseline (CVC 150 mg – placebo)			(–0.20, 0.18)			
APRI						
All subjects						
no.	114	114	114	112	112	112
Median (min, max)	0.470 (0.20, 3.12)	0.539 (0.15, 3.45)	0.024 (–1.30, 1.49)	0.568 (0.15, 2.26)	0.538 (0.13, 3.71)	–0.031 (–0.82, 3.46)
95% CI for difference in change from baseline (CVC 150 mg – placebo)			(–0.06, 0.17)			
Subjects with improvement						
no.	31	31	31	23	23	23
Mean (SD)	0.52 (0.29)	0.57 (0.49)	0.05 (0.41)	0.51 (0.26)	0.42 (0.26)	–0.09 (0.26)

95% CI for difference in change from baseline (CVC 150 mg – placebo)			(–0.05, 0.34)			
Subjects without improvement						
no.	83	83	83	92	92	92
Mean (SD)	0.61 (0.43)	0.72 (0.50)	0.11 (0.38)	0.70 (0.41)	0.81 (0.71)	0.11 (0.61)
95% CI for difference in change from baseline (CVC 150 mg – placebo)			(–0.15, 0.16)			
ELF						
All subjects						
no.	115	115	115	109	109	109
Median (min, max)	–0.892 (–2.70, 1.27)	–0.828 (–2.50, 1.08)	0.023 (–1.98, 1.65)	–0.893 (–2.20, 1.62)	–1.003 (–2.53, 2.07)	–0.113 (–1.21, 1.60)

95% CI for difference in change from baseline (CVC 150 mg – placebo)			(–0.05, 0.25)			
Subjects with improvement						
no.	33	33	33	23	23	23
Mean (SD)	–1.06 (0.65)	–1.10 (0.60)	–0.04 (0.66)	–1.10 (0.73)	–1.12 (0.68)	–0.02 (0.44)
95% CI for difference in change from baseline (CVC 150 mg – placebo)			(–0.34, 0.29)			
Subjects without improvement						
no.	82	82	82	89	89	89
Mean (SD)	–0.72 (0.73)	–0.66 (0.76)	0.06 (0.53)	–0.74 (0.73)	–0.81 (0.84)	–0.08 (0.59)

95% CI for difference in change from baseline (CVC 150 mg – placebo)	(–0.04, 0.30)

*APRI denotes aspartate aminotransferase-to-platelet ratio index, CI confidence intervals, ELF enhanced liver fibrosis, FIB-4 fibrosis-4, mITT modified intent-to-treat, NFS nonalcoholic fatty liver disease fibrosis score, PP per protocol, and SD standard deviation.

Table S7. Incidence of Treatment-Emergent Adverse Events and Laboratory Abnormalities per Treatment Group

no. (%)	CVC 150 mg (N = 144)	Placebo (N = 144)
Drug-related TEAEs[a]	61 (42.4)	54 (37.5)
Mild (grade 1)	29 (20.1)	34 (23.6)
Moderate (grade 2)	20 (13.9)	11 (7.6)
Severe (grade 3)	12 (8.3)	9 (6.3)
Life-threatening (grade 4)	0 (0)	0 (0)
Drug-related, clinical TEAEs of grade ≥2 severity observed in ≥2% of subjects		
Fatigue	4 (2.8)	1 (0.7)
Diarrhea	3 (2.1)	1 (0.7)
Headache	2 (1.4)	5 (3.5)
AEs leading to discontinuation	9 (6.3)	10 (6.9)
Serious adverse events[b]	16 (11.1)	10 (6.9)
Deaths	0 (0)	0 (0)
Grade 3 and 4 abnormal clinical laboratory results (≥2% of subjects in any treatment group)		
Fasting glucose		
Grade 3: >250–500 mg/dL	17 (11.9)	13 (9.2)
Grade 4: >500 mg/dL	…[c]	…[c]
ALT		
Grade 3: >5.0–20.0 × ULN	17 (11.8)	17 (11.8)

Grade 4: >20.0 × ULN	…[c]	…[c]
AST		
Grade 3: >5.0–20.0 × ULN	7 (4.9)	10 (6.9)
Grade 4: >20.0 × ULN	…[c]	…[c]
APT/PTT		
Grade 3: >2.5 × ULN	4 (2.8)	2 (1.4)
Triglycerides		
Grade 3: >500–1000 mg/dL	5 (3.5)	7 (4.9)
Grade 4: >1000 mg/dL	3 (2.1)	3 (2.1)
GGT		
Grade 3: >5.0–20.0 × ULN	8 (5.6)	6 (4.2)
Grade 4: >20.0 × ULN	1 (0.7)	1 (0.7)
Creatine kinase		
Grade 3: >5.0–10.0 × ULN	6 (4.2)	7 (4.9)
Grade 4: >10.0 × ULN	2 (1.4)	2 (1.4)
Uric acid		
Grade 3: (ULN – 10 mg/dL; ULN – 0.59 mol/L)[d]	9 (6.3)	9 (6.3)
Grade 4: >10 mg/dL	11 (7.6)	6 (4.2)
Amylase		
Grade 3: >2.0–5.0 × ULN	6 (4.2)	1 (0.7)
Grade 4: >5.0 × ULN	…[c]	…[c]
Phosphorus		
Grade 3: <2.0–1.0 mg/dL	5 (3.5)	2 (1.4)

Grade 4: <1.0 mg/dL	…[c]	…[c]
Absolute neutrophil		
Grade 3: <1.0–0.5 × 10^9/L	2 (1.4)	3 (2.1)
Grade 4: <0.5 × 10^9/L	2 (1.4)	1 (0.7)

AE, adverse event; ALT, alanine aminotransferase; APT, activated partial thromboplastin; AST, aspartate aminotransferase; CVC, cenicriviroc; GGT, gamma-glutamyl transferase; PTT, partial thromboplastin time; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

[a]An AE was considered related, as assessed by the investigator, if a temporal relationship between AE onset and administration of study drug existed, which could be readily explained by the subject's clinical state or by concomitant therapy.

[b]All treatment-emergent serious adverse events but one (grade 2 arrhythmia; subject remained on blinded treatment) were considered not related to treatment.

[c]One or more groups had zero cases; to maintain the blind, data that could be traced to an individual subject were omitted.

[d]With physiological consequences.

V. References

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