

Dataset Integrity Check for the
Cysteamine Bitartrate Delayed-Release
for the Treatment of Nonalcoholic Fatty
Liver Disease (NAFLD) in Children (CyNCh)
Data Files

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1 Standard Disclaimer

The intent of this DSIC is to provide confidence that the data distributed by the NIDDK repository is a true copy of the study data. Our intent is not to assess the integrity of the statistical analyses reported by study investigators. As with all statistical analyses of complex datasets, complete replication of a set of statistical results should not be expected in secondary analysis. This occurs for a number of reasons including differences in the handling of missing data, restrictions on cases included in samples for a particular analysis, software coding used to define complex variables, etc. Experience suggests that most discrepancies can ordinarily be resolved by consultation with the study data coordinating center (DCC), however this process is labor-intensive for both DCC and Repository staff. It is thus not our policy to resolve every discrepancy that is observed in an integrity check. Specifically, we do not attempt to resolve minor or inconsequential discrepancies with published results or discrepancies that involve complex analyses, unless NIDDK Repository staff suspect that the observed discrepancy suggests that the dataset may have been corrupted in storage, transmission, or processing by repository staff. We do, however, document in footnotes to the integrity check those instances in which our secondary analyses produced results that were not fully consistent with those reported in the target publication.

2 Study Background

The CyNCh (Cysteamine Bitartrate Delayed-Release for the Treatment of NAFLD in Children) study is a prospective, multicenter, double-blind clinical trial designed by the NASH Clinical Research Network to determine whether treatment with cysteamine improves disease severity in children diagnosed with NAFLD. Children between the ages of 8 and 17 years with biopsy-confirmed moderate to severe NAFLD were eligible for the CyNCh study. Participants were enrolled and randomized to treatment with either delayed-release cysteamine bitartrate capsules or placebo capsules. Improvement in NAFLD at 52 weeks, defined as a decrease in NAFLD Activity Score (NAS) of at least 2 and no worsening of fibrosis, will be assessed as the primary outcome measure. Secondary outcome measures, also to be assessed at 52 weeks, include reduction in serum aminotransferase and gamma-glytamyl transpeptidase, reduction in MRI-determined hepatic fat fraction, changes in markers of oxidation and anti-oxidant status, changes in histology and symptoms, and quality of life.

3 Archived Datasets

All SAS data files, as provided by the Data Coordinating Center (DCC), are located in the data package. For this replication, variables were taken from the various analysis datasets.

4 Statistical Methods

Analyses were performed to duplicate results for the data published by Schwimmer et al in Gastroenterology in 2016 [1].

To verify the integrity of the three datasets, descriptive statistics were computed.

5 Results

For Table 1 in the publication [1], Baseline Characteristics of the Study Population, Table A lists the variables that were used in the replication and Table B compares the results calculated from the archived data file to the results published in Table 1. The results of the replication are an exact match to the published results.

For Table 2 in the publication [1], Changes in Histologic Features of the Liver After 52 Weeks of Treatment, Table C lists the variables that were used in the replication and Table D compares the results calculated from the archived data file to the results published in Table 2. The results of the replication are an exact match to the published results.

For Table 3 in the publication [1], Changes in Liver Enzyme Levels, Serum Biochemical Tests, Metabolic Factors, and Quality of Life From Baseline to 52 Weeks, Table E lists the variables that were used in the replication and Table F compares the results calculated from the archived data file to the results published in Table 3. The results of the replication are an exact match to the published results.

For Table 4 in the publication [1], Changes in Histologic Features of the Liver After 52 Weeks of Treatment in Patients Weighing ≤ 65 kg vs > 65 kg, Table G lists the variables that were used in the replication and Table H compares the results calculated from the archived data file to the results published in Table 4. The results of the replication are an exact match to the published results.

For Table 5 in the publication [1], Adverse Events by Body System, Table I lists the variables that were used in the replication and Table J compares the results calculated from the archived data file to the results published in Table 5. The results of the replication are an exact match to the published results.

6 Conclusions

The NIDDK repository is confident that the CyNCh data files to be distributed are a copy of the manuscript data.

7 References

[1] Schwimmer, J.B., Lavine, J.E., Wilson, L.A., Neuschwander-Tetri, B.A., Xanthakos, S.A., Kohli, R., Barlow, S.E., Vos, M.B., Karpen, S.J., Molleston, J.P., Whittington, P.F., Rosenthal, P., Jain, A.K., Murray, K.F., Brunt, E.M., Kleiner, D.E., Van Natta, M.L., Clark, J.M., Tonascia, J., Doo, E., and the NASH CRN. In Children With Nonalcoholic Fatty Liver Disease, Cysteamine Bitartrate Delayed Release Improves Liver Enzymes but Does Not Reduce Disease Activity Scores. *Gastroenterology* 2016;151:1141-1154.

Table A: Variables used to replicate Table 1: Baseline Characteristics of the Study Population

Table Variable	dataset.variable
Weight stratum	table1.wt_strat
Age, y	table1.age
Male	table1.gender
Race	table1.race
Hispanic ethnicity	table1.hispanic
Self-reported pediatric QOL Physical health	table1.cphys
Self-reported pediatric QOL Psychosocial health	table1.csoc
Parent/guardian-reported pediatric QOL Physical health	table1.pphys
Parent/guardian-reported pediatric QOL Psychosocial health	table1.psoc
Alanine aminotransferase, U/L	table1.alt
Aspartate aminotransferase, U/L	table1.ast
Alkaline phosphatase, U/L	table1.alkphos
Gamma-glutamyl transpeptidase, U/L	table1.ggt
Total bilirubin, mg/dL	table1.bilitot
Total cholesterol, mg/dL	table1.totchol
HDL cholesterol, mg/dL	table1.hdl
LDL cholesterol, mg/dL	table1.ldl
Non-HDL cholesterol, mg/dL	table1.nonhdlc
Triglycerides, mg/dL	table1.triglyc
Weight, kg	table1.wtkg
Body mass index, kg/m ²	table1.bmi
Body mass index z-score	table1.bmiz
Waist circumference, cm	table1.waistcm
Fasting serum glucose, mg/dL	table1.glucose
Insulin, uU/mL	table1.insulin
HOMA-IR (glucose [mmol/L] x insulin [pmol/L]/22.5)	table1.homa
Systolic blood pressure, mm Hg	table1.systolic
Diastolic blood pressure, mm Hg	table1.diastoli
Diabetes	table1.diabetes
Hypertension	table1.hyperten
Hyperlipidemia	table1.hyperlip
NAFLD activity score	table1.bnas
Steatosis score	table1.bsteato
Lobular inflammation score	table1.blobinf
Hepatocellular ballooning score	table1.bball
Portal inflammation score	table1.bportinf
Fibrosis stage (0, 1a, 1b, 1c, 2, 3, 4)	table1.bfib

Table Variable	dataset.variable
Fibrosis stage (0, 1, 2, 3, 4)	table1.bfibro
Steatohepatitis	table1.bstdiag
Treatment	table1.tx

Table B: Comparison of values computed in integrity check to reference article Table 1 values

	CBDR (N=88) Manuscript	CBDR (N=88) DSIC	Diff. (N=0)	Placebo (N=81) Manuscript	Placebo (N=81) DSIC	Diff. (N=0)
Weight stratum						
≤65 kg	24 (27%)	24 (27%)	0 (0%)	23 (28%)	23 (28%)	0 (0%)
>65 to 80 kg	14 (16%)	14 (16%)	0 (0%)	10 (12%)	10 (12%)	0 (0%)
>80 kg	50 (57%)	50 (57%)	0 (0%)	48 (59%)	48 (59%)	0 (0%)
Demographics						
Age, y	13.8 (2.9)	13.8 (2.9)	0 (0)	13.6 (2.5)	13.6 (2.5)	0 (0)
Male	63 (72%)	63 (72%)	0 (0%)	56 (69%)	56 (69%)	0 (0%)
Race						
American Indian/Alaska Native	5 (6%)	5 (6%)	0 (0%)	6 (7%)	6 (7%)	0 (0%)
Asian	0 (0%)	0 (0%)	0 (0%)	2 (2%)	2 (2%)	0 (0%)
Black or African American	3 (3%)	3 (3%)	0 (0%)	3 (4%)	3 (4%)	0 (0%)
White	56 (64%)	56 (64%)	0 (0%)	46 (57%)	46 (57%)	0 (0%)
More than 1 race	3 (3%)	3 (3%)	0 (0%)	1 (1%)	1 (1%)	0 (0%)
Refusal/not stated	21 (24%)	21 (24%)	0 (0%)	23 (28%)	23 (28%)	0 (0%)
Hispanic ethnicity	66 (75%)	66 (75%)	0 (0%)	58 (72%)	58 (72%)	0 (0%)
Self-reported pediatric QOL						
Physical health	81 (15)	81 (15)	0 (0)	82 (19)	82 (19)	0 (0)
Psychosocial health	75 (16)	75 (16)	0 (0)	77 (16)	77 (16)	0 (0)
Parent/guardian-reported pediatric QOL						
Physical health	68 (21)	68 (21)	0 (0)	69 (24)	69 (24)	0 (0)
Psychosocial health	67 (19)	67 (19)	0 (0)	68 (18)	68 (18)	0 (0)
Liver enzyme levels						
Alanine aminotransferase, U/L						
Median (IQR)	93 (67-175)	93 (67-175)	0 (0-0)	80 (61-120)	80 (61-120)	0 (0-0)
Mean (SD)	140 (118)	140 (118)	0 (0)	103 (76)	103 (76)	0 (0)
Aspartate aminotransferase, U/L						

	CBDR (N=88) Manuscript	CBDR (N=88) DSIC	Diff. (N=0)	Placebo (N=81) Manuscript	Placebo (N=81) DSIC	Diff. (N=0)
Median (IQR)	55 (40-91)	55 (40-91)	0 (0-0)	49 (38-69)	49 (38-69)	0 (0-0)
Mean (SD)	82 (71)	82 (71)	0 (0)	59 (38)	59 (38)	0 (0)
Alkaline phosphatase, U/L	224 (116)	224 (116)	0 (0)	214 (101)	214 (101)	0 (0)
Gamma-glutamyl transpeptidase, U/L	50 (33)	50 (33)	0 (0)	44 (29)	44 (29)	0 (0)
Total bilirubin, mg/dL	0.54 (0.34)	0.54 (0.34)	0 (0)	0.50 (0.26)	0.50 (0.26)	0 (0)
Lipids						
Total cholesterol, mg/dL	165 (40)	165 (40)	0 (0)	163 (37)	163 (37)	0 (0)
HDL cholesterol, mg/dL	39 (9)	39 (9)	0 (0)	41 (9)	41 (9)	0 (0)
LDL cholesterol, mg/dL	95 (32)	95 (32)	0 (0)	92 (31)	92 (31)	0 (0)
Non-HDL cholesterol, mg/dL	126 (40)	126 (40)	0 (0)	122 (37)	122 (37)	0 (0)
Triglycerides, mg/dL	160 (81)	160 (81)	0 (0)	157 (77)	157 (77)	0 (0)
Metabolic factors						
Weight, kg	85 (26)	85 (26)	0 (0)	84 (25)	84 (25)	0 (0)
Body mass index, kg/m ²	33 (7)	33 (7)	0 (0)	32 (6)	32 (6)	0 (0)
Body mass index z-score	2.2 (0.5)	2.2 (0.5)	0 (0)	2.2 (0.4)	2.2 (0.4)	0 (0)
Waist circumference, cm	104 (15)	104 (15)	0 (0)	103 (15)	103 (15)	0 (0)
Fasting serum glucose, mg/dL	87 (10)	87 (10)	0 (0)	88 (14)	88 (14)	0 (0)
Insulin, uU/mL	35 (31)	35 (31)	0 (0)	38 (34)	38 (34)	0 (0)
HOMA-IR (glucose [mmol/L] x insulin [pmol/L]/22.5)	7.7 (7.5)	7.7 (7.5)	0 (0)	8.4 (7.7)	8.4 (7.7)	0 (0)
Systolic blood pressure, mm Hg	120 (11)	120 (11)	0 (0)	120 (12)	120 (12)	0 (0)
Diastolic blood pressure, mm Hg	68 (8)	68 (8)	0 (0)	67 (10)	67 (10)	0 (0)
Comorbidities						
Diabetes	1 (1%)	1 (1%)	0 (0%)	7 (9%)	7 (9%)	0 (0%)
Hypertension	9 (10%)	9 (10%)	0 (0%)	6 (7%)	6 (7%)	0 (0%)
Hyperlipidemia	13 (15%)	13 (15%)	0 (0%)	12 (15%)	12 (15%)	0 (0%)
Liver histology findings						
NAFLD activity score	4.7 (1.4)	4.7 (1.4)	0 (0)	4.6 (1.4)	4.6 (1.4)	0 (0)
Steatosis score	2.3 (0.8)	2.3 (0.8)	0 (0)	2.5 (0.7)	2.5 (0.7)	0 (0)
Lobular inflammation score	1.8 (0.7)	1.8 (0.7)	0 (0)	1.6 (0.7)	1.6 (0.7)	0 (0)
Hepatocellular ballooning score	0.6 (0.7)	0.6 (0.7)	0 (0)	0.6 (0.8)	0.6 (0.8)	0 (0)
Portal inflammation score	1.1 (0.5)	1.1 (0.5)	0 (0)	1.1 (0.5)	1.1 (0.5)	0 (0)

	CBDR (N=88) Manuscript	CBDR (N=88) DSIC	Diff. (N=0)	Placebo (N=81) Manuscript	Placebo (N=81) DSIC	Diff. (N=0)
Fibrosis stage						
0, none	24 (27%)	24 (27%)	0 (0%)	25 (31%)	25 (31%)	0 (0%)
1a, mild, zone 3 perisinusoidal	9 (10%)	9 (10%)	0 (0%)	7 (9%)	7 (9%)	0 (0%)
1b, moderate, zone 3 perisinusoidal	6 (7%)	6 (7%)	0 (0%)	5 (6%)	5 (6%)	0 (0%)
1c, portal/peripoportal only	20 (23%)	20 (23%)	0 (0%)	20 (25%)	20 (25%)	0 (0%)
2, zone 3 and periportal, any combination	9 (10%)	9 (10%)	0 (0%)	13 (16%)	13 (16%)	0 (0%)
3, bridging	19 (22%)	19 (22%)	0 (0%)	11 (14%)	11 (14%)	0 (0%)
4, cirrhosis	1 (1%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Fibrosis stage	1.3 (1.1)	1.3 (1.1)	0 (0)	1.1 (1.0)	1.1 (1.0)	0 (0)
Steatohepatitis						
No	25 (28%)	25 (28%)	0 (0%)	19 (23%)	19 (23%)	0 (0%)
Borderline zone 3 pattern	16 (18%)	16 (18%)	0 (0%)	10 (12%)	10 (12%)	0 (0%)
Borderline zone 1 pattern	23 (26%)	23 (16%)	0 (0%)	29 (36%)	29 (36%)	0 (0%)
Definite	24 (27%)	24 (27%)	0 (0%)	23 (28%)	23 (28%)	0 (0%)

	Total (N=169) Manuscript	Total (N=169) DSIC	Diff. (N=0)
Weight stratum			
≤65 kg	47 (28%)	47 (28%)	0 (0%)
>65 to 80 kg	24 (14%)	24 (14%)	0 (0%)
>80 kg	98 (58%)	98 (58%)	0 (0%)
Demographics			
Age, y	13.7 (2.7)	13.7 (2.7)	0 (0)
Male	119 (70%)	119 (70%)	0 (0%)
Race			
American Indian/Alaska Native	11 (7%)	11 (7%)	0 (0%)
Asian	2 (1%)	2 (1%)	0 (0%)
Black or African American	6 (4%)	6 (4%)	0 (0%)
White	102 (60%)	102 (60%)	0 (0%)
More than 1 race	4 (2%)	4 (2%)	0 (0%)

	Total (N=169) Manuscript	Total (N=169) DSIC	Diff. (N=0)
Refusal/not stated	44 (26%)	44 (26%)	0 (0%)
Hispanic ethnicity	124 (73%)	124 (73%)	0 (0%)
Self-reported pediatric QOL			
Physical health	81 (17)	81 (17)	0 (0)
Psychosocial health	76 (16)	76 (16)	0 (0)
Parent/guardian-reported pediatric QOL			
Physical health	68 (23)	68 (23)	0 (0)
Psychosocial health	68 (19)	68 (19)	0 (0)
Liver enzyme levels			
Alanine aminotransferase, U/L			
Median (IQR)	87 (62-151)	87 (62-151)	0 (0-0)
Mean (SD)	123 (101)	123 (101)	0 (0)
Aspartate aminotransferase, U/L			
Median (IQR)	52 (39-79)	52 (39-79)	0 (0-0)
Mean (SD)	71 (59)	71 (59)	0 (0)
Alkaline phosphatase, U/L	220 (109)	220 (109)	0 (0)
Gamma-glutamyl transpeptidase, U/L	47 (31)	47 (31)	0 (0)
Total bilirubin, mg/dL	0.52 (0.30)	0.52 (0.30)	0 (0)
Lipids			
Total cholesterol, mg/dL	164 (38)	164 (38)	0 (0)
HDL cholesterol, mg/dL	40 (9)	40 (9)	0 (0)
LDL cholesterol, mg/dL	94 (31)	94 (31)	0 (0)
Non-HDL cholesterol, mg/dL	124 (39)	124 (39)	0 (0)
Triglycerides, mg/dL	158 (79)	158 (79)	0 (0)
Metabolic factors			
Weight, kg	85 (25)	85 (25)	0 (0)
Body mass index, kg/m ²	32 (6)	32 (6)	0 (0)
Body mass index z-score	2.2 (0.4)	2.2 (0.4)	0 (0)
Waist circumference, cm	103 (15)	103 (15)	0 (0)
Fasting serum glucose, mg/dL	88 (12)	88 (12)	0 (0)
Insulin, uU/mL	36 (32)	36 (32)	0 (0)

	Total (N=169) Manuscript	Total (N=169) DSIC	Diff. (N=0)
HOMA-IR (glucose [mmol/L] x insulin [pmol/L]/22.5)	8.0 (7.6)	8.0 (7.6)	0 (0)
Systolic blood pressure, mm Hg	120 (11)	120 (11)	0 (0)
Diastolic blood pressure, mm Hg	67 (9)	67 (9)	0 (0)
Comorbidities			
Diabetes	8 (5%)	8 (5%)	0 (0%)
Hypertension	15 (9%)	15 (9%)	0 (0%)
Hyperlipidemia	25 (15%)	25 (15%)	0 (0%)
Liver histology findings			
NAFLD activity score	4.7 (1.4)	4.7 (1.4)	0 (0)
Steatosis score	2.4 (0.7)	2.4 (0.7)	0 (0)
Lobular inflammation score	1.7 (0.7)	1.7 (0.7)	0 (0)
Hepatocellular ballooning score	0.6 (0.7)	0.6 (0.7)	0 (0)
Portal inflammation score	1.1 (0.5)	1.1 (0.5)	0 (0)
Fibrosis stage			
0, none	49 (29%)	49 (29%)	0 (0%)
1a, mild, zone 3 perisinusoidal	16 (9%)	16 (9%)	0 (0%)
1b, moderate, zone 3 perisinusoidal	11 (7%)	11 (7%)	0 (0%)
1c, portal/peroportal only	40 (24%)	40 (24%)	0 (0%)
2, zone 3 and periportal, any combination	22 (13%)	22 (13%)	0 (0%)
3, bridging	30 (18%)	30 (18%)	0 (0%)
4, cirrhosis	1 (1%)	1 (1%)	0 (0%)
Fibrosis stage	1.2 (1.1)	1.2 (1.1)	0 (0)
Steatohepatitis			
No	44 (26%)	44 (26%)	0 (0%)
Borderline zone 3 pattern	26 (15%)	26 (15%)	0 (0%)
Borderline zone 1 pattern	52 (31%)	52 (31%)	0 (0%)
Definite	47 (28%)	47 (28%)	0 (0%)

Table C: Variables used to replicate Table 2: Changes in Histologic Features of the Liver After 52 Weeks of Treatment

Table Variable	dataset.variable
Histologic improvement: Primary outcome	
Patients with improvement	table2.improve2
Histologic improvement: Completed follow-up evaluation	
Patients with improvement	table2.improve
NAFLD activity score	
Change in score	table2.fnas, table2.bnass
Steatosis	
Patients with improvement	table2.impstea0
Change in score	table2.fsteato, table2.bsteato
Lobular inflammation	
Patients with improvement	table2.implobi0
Change in score	table2.flobinf, table2.blobinf
Hepatocellular ballooning	
Patients with improvement	table2.impball2
Change in score	table2.fball, table2.bball
Portal inflammation	
Patients with improvement	table2.impport0
Change in score	table2.fportinf, table2.bportinf
Fibrosis	
Patients with improvement	table2.impfib2
Change in score	table2.ffib. table2.bfib
Resolution of NASH	table2.resolve2
Treatment	table2.cyst

Table D: Comparison of values computed in integrity check to reference article Table 2 values

	CBDR Manuscript	CBDR DSIC	Diff.	Placebo Manuscript	Placebo DSIC	Diff.
Histologic improvement: Primary outcome						
Patients, n	88	88	0	81	81	0
Patients with improvement	25 (28%)	25 (28%)	0 (0%)	18 (22%)	18 (22%)	0 (0%)
Histologic improvement: Completed follow-up evaluation						
Patients, n	71	71	0	75	75	0
Patients with improvement	25 (35%)	25 (35%)	0 (0%)	18 (24%)	18 (24%)	0 (0%)
Changes from baseline in histologic features						
NAFLD activity score						
Change in score	-0.8 ± 1.8	-0.8 ± 1.8	0 ± 0	-0.8 ± 1.8	-0.8 ± 1.8	0 ± 0
Steatosis						
Patients with improvement	26 (30%)	26 (30%)	0 (0%)	33 (41%)	33 (41%)	0 (0%)
Change in score	-0.3 ± 0.9	-0.3 ± 0.9	0 ± 0	-0.4 ± 0.9	-0.4 ± 0.9	0 ± 0
Lobular inflammation						
Patients with improvement	32 (36%)	32 (36%)	0 (0%)	17 (21%)	17 (21%)	0 (0%)
Change in score	-0.4 ± 0.8	-0.4 ± 0.8	0 ± 0	-0.1 ± 0.8	-0.1 ± 0.8	0 ± 0
Hepatocellular ballooning						
Patients with improvement	17 (19%)	17 (19%)	0 (0%)	21 (26%)	21 (26%)	0 (0%)
Change in score	-0.1 ± 0.7	0.1 ± 0.7	0 ± 0	0.3 ± 0.8	-0.3 ± 0.8	0 ± 0
Portal inflammation						
Patients with improvement	18 (20%)	18 (20%)	0 (0%)	14 (17%)	14 (17%)	0 (0%)
Change in score	-0.1 ± 0.6	-0.1 ± 0.6	0 ± 0	-0.1 ± 0.6	-0.1 ± 0.6	0 ± 0
Fibrosis						
Patients with improvement	25 (28%)	25 (28%)	0 (0%)	23 (28%)	23 (28%)	0 (0%)
Change in score	-0.3 ± 0.9	-0.3 ± 0.9	0 ± 0	-0.1 ± 1.0	-0.1 ± 1.0	0 ± 0
Resolution of NASH	4 (17%)	4 (17%)	0 (0%)	2 (9%)	2 (9%)	0 (0%)

Table E: Variables used to replicate Table 3: Changes in Liver Enzyme Levels, Serum Biochemical Tests, Metabolic Factors, and Quality of Life From Baseline to 52 Weeks

Table Variable	dataset.variable
ALT, U/L	table3.alt_d
AST, U/L	table3.ast_d
Alkaline phosphatase, U/L	table3.alkphos1
Gamma-glutamyl transpeptidase, U/L	table3.ggt_d
Total cholesterol, mg/dL	table3.totchol1
HDL cholesterol, mg/dL	table3.hdl_d
LDL cholesterol, mg/dL	table3.ldl_d
Non-HDL cholesterol, mg/dL	table3.nonhdlc1
Triglycerides, mg/dL	table3.triglyc1
Weight, kg	table3.wtkg_d
Body mass index, kg/m ²	table3.bmi_d
Body mass index z-score	table3.bmiz_d
Waist circumference, cm	table3.waistcm1
Fasting serum glucose, mg/dL	table3.glucose1
Insulin, uU/mL	table3.insulin1
HOMA-IR (glucose [mmol/L] x insulin [pmol/L]/22.5)	table3.homa_d
Systolic blood pressure, mm Hg	table3.systoli1
Diastolic blood pressure, mm Hg	table3.diastol1
Self-reported pediatric QOL Physical health	table3.cphys_d
Self-reported pediatric QOL Psychosocial health	table3.csoc_d
Parent/guardian-reported pediatric QOL Physical health	table3.pphys_d
Parent/guardian-reported pediatric QOL Psychosocial health	table3.psoc_d
Treatment	table3.tx

Table F: Comparison of values computed in integrity check to reference article Table 3 values

	CBDR (N=75) Manuscript	CBDR (N=76) DSIC	Diff. (N=1)	Placebo (N=77) Manuscript	Placebo (N=77) DSIC	Diff. (N=0)
Liver enzyme levels						
ALT, U/L	-53 (88)	-53 (88)	0 (0)	-8 (77)	-8 (77)	0 (0)
AST, U/L	-31 (52)	-31 (52)	0 (0)	-4 (36)	-4 (36)	0 (0)
Alkaline phosphatase, U/L	-31 (70)	-31 (70)	0 (0)	-19 (54)	-19 (54)	0 (0)
Gamma-glutamyl transpeptidase, U/L	-10 (23)	-10 (23)	0 (0)	-1 (16)	-1 (16)	0 (0)
Lipids						
Total cholesterol, mg/dL	-11 (23)	-11 (23)	0 (0)	-4 (22)	-4 (22)	0 (0)
HDL cholesterol, mg/dL	0.0 (6.2)	0.0 (6.2)	0 (0)	-0.4 (7.6)	-0.4 (7.6)	0 (0)
LDL cholesterol, mg/dL	-10 (19)	-10 (19)	0 (0)	-3 (20)	-3 (20)	0 (0)
Non-HDL cholesterol, mg/dL	-11 (22)	-11 (22)	0 (0)	-4 (19)	-4 (19)	0 (0)
Triglycerides, mg/dL	-7 (60)	-7 (60)	0 (0)	0 (68)	0 (68)	0 (0)
Metabolic factors						
Weight, kg	6.3 (9.3)	6.3 (9.3)	0 (0)	7.8 (6.6)	7.8 (6.6)	0 (0)
Body mass index, kg/m ²	0.8 (2.8)	0.8 (2.8)	0 (0)	1.1 (2.2)	1.1 (2.2)	0 (0)
Body mass index z-score	-0.1 (0.3)	-0.1 (0.3)	0 (0)	0 (0.2)	0 (0.2)	0 (0)
Waist circumference, cm	2.5 (7.7)	2.5 (7.7)	0 (0)	2.3 (7.5)	2.3 (7.5)	0 (0)
Fasting serum glucose, mg/dL	1 (12)	1 (12)	0 (0)	5 (27)	5 (27)	0 (0)
Insulin, uU/mL	6 (36)	6 (36)	0 (0)	10 (40)	10 (40)	0 (0)
HOMA-IR (glucose [mmol/L] x insulin [pmol/L]/22.5)	1.4 (9.2)	1.4 (9.2)	0 (0)	3.6 (12.5)	3.6 (12.5)	0 (0)
Systolic blood pressure, mm Hg	3 (12)	3 (12)	0 (0)	2 (12)	2 (12)	0 (0)
Diastolic blood pressure, mm Hg	-1 (9)	-1 (9)	0 (0)	1 (9)	1 (9)	0 (0)
Self-reported pediatric QOL						
Physical health	4 (17)	4 (17)	0 (0)	5 (16)	5 (16)	0 (0)
Psychosocial health	4 (15)	4 (15)	0 (0)	5 (14)	5 (14)	0 (0)
Parent/guardian-reported pediatric QOL						
Physical health	4 (27)	4 (27)	0 (0)	5 (24)	5 (24)	0 (0)
Psychosocial health	5 (18)	5 (18)	0 (0)	6 (24)	6 (24)	0 (0)

Table G: Variables used to replicate Table 4: Changes in Histologic Features of the Liver After 52 Weeks of Treatment in Patients Weighing ≤ 65 kg vs > 65 kg

Table Variable	dataset.variable
Primary outcome	
Patients with improvement	table4.improve2
Completed follow-up evaluation	
Patients with improvement	table4.improve
Adherent to prescribed dose of study medication	
Patients with improvement	table4.improve2, table4.adherent
NAFLD activity score	
Change in score	table4.dnas
Steatosis	
Patients with improvement	table4.impsteat
Change in score	table4.dsteato
Lobular inflammation	
Patients with improvement	table4.implobin
Change in score	table4.dlobinf
Hepatocellular ballooning	
Patients with improvement	table4.impball2
Change in score	table4.dball
Portal inflammation	
Patients with improvement	table4.impporti
Change in score	table4.dportinf
Fibrosis	
Patients with improvement	table4.impfib2
Change in score	table4.dfib
Change in ALT, U/L	table4.alt_d
Change in AST, U/L	table4.ast_d
Change in BMI z-score	table4.bmiz_d
Treatment	table4.tx
Weight group	table4.wt_bin

Table H: Comparison of values computed in integrity check to reference article Table 4 values

≤ 65 kg

	CBDR Manuscript	CBDR DSIC	Diff.	Placebo Manuscript	Placebo DSIC	Diff.
Primary outcome						
Patients, n	24	24	0	23	23	0
Patients with improvement	12 (50%)	12 (50%)	0 (0%)	3 (13%)	3 (13%)	0 (0%)
Completed follow-up evaluation						
Patients, n	21	21	0	21	21	0
Patients with improvement	12 (57%)	12 (57%)	0 (0%)	3 (14%)	3 (14%)	0 (0%)
Adherent to prescribed dose of study medication						
Patients, n	9	9	0	15	15	0
Patients with improvement	5 (56%)	5 (56%)	0 (0%)	2 (13%)	2 (13%)	0 (0%)
Changes from baseline in histologic features						
NAFLD activity score						
Change in score	-1.7 ± 1.6	-1.7 ± 1.6	0 ± 0	-0.8 ± 1.3	-0.8 ± 1.3	0 ± 0
Steatosis						
Patients with improvement	12 (50%)	12 (50%)	0 (0%)	11 (48%)	11 (48%)	0 (0%)
Change in score	-0.7 ± 1.1	-0.7 ± 1.1	0 ± 0	-0.6 ± 0.9	-0.6 ± 0.9	0 ± 0
Lobular inflammation						
Patients with improvement	13 (54%)	13 (54%)	0 (0%)	5 (22%)	5 (22%)	0 (0%)
Change in score	-0.7 ± 0.8	-0.7 ± 0.8	0 ± 0	-0.1 ± 0.7	-0.1 ± 0.7	0 ± 0
Hepatocellular ballooning						
Patients with improvement	8 (33%)	8 (33%)	0 (0%)	1 (4%)	1 (4%)	0 (0%)
Change in score	-0.3 ± 0.8	-0.3 ± 0.8	0 ± 0	0.0 ± 0.3	0.0 ± 0.3	0 ± 0
Portal inflammation						
Patients with improvement	8 (33%)	8 (33%)	0 (0%)	5 (22%)	5 (22%)	0 (0%)
Change in score	-0.2 ± 0.7	-0.2 ± 0.7	0 ± 0	-0.2 ± 0.7	-0.2 ± 0.7	0 ± 0
Fibrosis						
Patients with improvement	10 (42%)	10 (42%)	0 (0%)	10 (43%)	10 (43%)	0 (0%)
Change in score	-0.4 ± 1.2	-0.4 ± 1.2	0 ± 0	-0.4 ± 1.0	-0.4 ± 1.0	0 ± 0
Changes from baseline in liver enzyme levels and BMI z-score						

	CBDR Manuscript	CBDR DSIC	Diff.	Placebo Manuscript	Placebo DSIC	Diff.
Number of patients	21	21	0	23	23	0
Change in ALT, U/L	-82 ± 119	-82 ± 119	0 ± 0	-23 ± 52	-23 ± 52	0 ± 0
Change in AST, U/L	-42 ± 61	-42 ± 61	0 ± 0	-11 ± 23	-11 ± 23	0 ± 0
Change in BMI z-score	-0.2 ± 0.2	-0.2 ± 0.2	0 ± 0	-0.1 ± 0.2	-0.1 ± 0.2	0 ± 0

> 65 kg

	CBDR Manuscript	CBDR DSIC	Diff.	Placebo Manuscript	Placebo DSIC	Diff.
Primary outcome						
Patients, n	64	64	0	58	58	0
Patients with improvement	13 (20%)	13 (20%)	0 (0%)	15 (26%)	15 (26%)	0 (0%)
Completed follow-up evaluation						
Patients, n	50	50	0	54	54	0
Patients with improvement	13 (26%)	13 (26%)	0 (0%)	15 (28%)	15 (28%)	0 (0%)
Adherent to prescribed dose of study medication						
Patients, n	20	20	0	25	25	0
Patients with improvement	5 (25%)	5 (25%)	0 (0%)	5 (20%)	5 (20%)	0 (0%)
Changes from baseline in histologic features						
NAFLD activity score						
Change in score	-0.4 ± 1.8	-0.4 ± 1.8	0 ± 0	-0.8 ± 2.0	-0.8 ± 2.0	0 ± 0
Steatosis						
Patients with improvement	14 (22%)	14 (22%)	0 (0%)	22 (38%)	22 (38%)	0 (0%)
Change in score	-0.1 ± 0.8	-0.1 ± 0.8	0 ± 0	-0.4 ± 0.9	-0.4 ± 0.9	0 ± 0
Lobular inflammation						
Patients with improvement	19 (30%)	19 (30%)	0 (0%)	12 (21%)	12 (21%)	0 (0%)
Change in score	-0.3 ± 0.8	-0.3 ± 0.8	0 ± 0	0.0 ± 0.8	0.0 ± 0.8	0 ± 0
Hepatocellular ballooning						
Patients with improvement	9 (14%)	9 (14%)	0 (0%)	20 (34%)	20 (34%)	0 (0%)
Change in score	0.0 ± 0.7	0.0 ± 0.7	0 ± 0	-0.4 ± 0.9	-0.4 ± 0.9	0 ± 0
Portal inflammation						
Patients with improvement	10 (16%)	10 (16%)	0 (0%)	9 (16%)	9 (16%)	0 (0%)
Change in score	0.0 ± 0.6	0.0 ± 0.6	0 ± 0	0.0 ± 0.6	0.0 ± 0.6	0 ± 0

	CBDR Manuscript	CBDR DSIC	Diff.	Placebo Manuscript	Placebo DSIC	Diff.
Fibrosis						
Patients with improvement	15 (23%)	15 (23%)	0 (0%)	13 (22%)	13 (22%)	0 (0%)
Change in score	-0.3 ± 0.8	-0.3 ± 0.8	0 ± 0	0.0 ± 0.9	0.0 ± 0.9	0 ± 0
Changes from baseline in liver enzyme levels and BMI z-score						
Number of patients	53	53	0	54	54	0
Change in ALT, U/L	-41 ± 71	-41 ± 71	0 ± 0	-2 ± 85	-2 ± 85	0 ± 0
Change in AST, U/L	-27 ± 48	-27 ± 48	0 ± 0	0 ± 39	0.0 ± 39	0 ± 0
Change in BMI z-score	0.0 ± 0.3	0.0 ± 0.3	0 ± 0	0.0 ± 0.2	0.0 ± 0.2	0 ± 0

Table I: Variables used to replicate Table 5: Adverse Events by Body System

Table Variable	dataset.variable
Auditory	table5.auditory
Allergy	table5.allergy
Ocular/visual	table5.ocular
Hepatobiliary/pancreas	table5.hepatobi
Infection	table5.infectio
Constitutional symptoms	table5.constitu
Psychiatric	table5.psychiat
Cardiovascular	table5.cardiova
Dermatological	table5.dermatol
Endocrine	table5.endocrin
Gastrointestinal	table5.gastroin
Lymphatic	table5.lymphati
Musculoskeletal/soft tissue	table5.musculos
Neurology	table5.neurolog
Pulmonary/upper respiratory	table5.pulmonar
Renal/genitourinary	table5.renal
Sexual	table5.sexual
Other	table5.othersys

Table Variable	dataset.variable
Total	table5.auditory, table5.allergy, table5.ocular, table5.hepatobi, table5.infectio, table5.constitu, table5.psychiat, table5.cardiova, table5.dermatol, table5.endocrin, table5.gastroin, table5.lymphati, table5.musculos, table5.neurolog, table5.pulmonar, table5.renal, table5.sexual, table5.othersys
Serious adverse event, all	table5.sae
Auditory, patients	table5_onrec.everaudi
Allergy, patients	table5_onrec.everalle
Ocular/visual, patients	table5_onrec.everocul
Hepatobiliary/pancreas, patients	table5_onrec.everhepa
Infection, patients	table5_onrec.everinfe
Constitutional symptoms, patients	table5_onrec.evercons
Psychiatric, patients	table5_onrec.everpsyc
Cardiovascular, patients	table5_onrec.evercard
Dermatological, patients	table5_onrec.everderm
Endocrine, patients	table5_onrec.everendo
Gastrointestinal, patients	table5_onrec.evergast
Lymphatic, patients	table5_onrec.everlymp
Musculoskeletal/soft tissue, patients	table5_onrec.evermusc
Neurology, patients	table5_onrec.everneur
Pulmonary/upper respiratory, patients	table5_onrec.everpulm
Renal/genitourinary, patients	table5_onrec.everrena
Sexual, patients	table5_onrec.eversexu
Other, patients	table5_onrec.everothe
Total, patients	table5_onrec.everaudi, table5_onrec.everalle, table5_onrec.everocul, table5_onrec.everhepa, table5_onrec.everinfe, table5_onrec.evercons, table5_onrec.everpsyc, table5_onrec.evercard, table5_onrec.everderm, table5_onrec.everendo, table5_onrec.evergast, table5_onrec.evermusc, table5_onrec.everlymp, table5_onrec.everneur, table5_onrec.everpulm, table5_onrec.everrena, table5_onrec.eversexu, table5_onrec.everothe
Auditory, patients, serious adverse event	table5_onrecsae.everaudi
Allergy, patients, serious adverse event	table5_onrecsae.everalle
Ocular/visual, patients, serious adverse event	table5_onrecsae.everocul
Hepatobiliary/pancreas, patients, serious adverse event	table5_onrecsae.everhepa

Table Variable	dataset.variable
Infection, patients, serious adverse event	table5_onerecsae.everinfe
Constitutional symptoms, patients, serious adverse event	table5_onerecsae.evercons
Psychiatric, patients, serious adverse event	table5_onerecsae.everpsyc
Cardiovascular, patients, serious adverse event	table5_onerecsae.evercard
Dermatological, patients, serious adverse event	table5_onerecsae.everderm
Endocrine, patients, serious adverse event	table5_onerecsae.everendo
Gastrointestinal, patients, serious adverse event	table5_onerecsae.evergast
Lymphatic, patients, serious adverse event	table5_onerecsae.everlymp
Musculoskeletal/soft tissue, patients, serious adverse event	table5_onerecsae.evermusc
Neurology, patients, serious adverse event	table5_onerecsae.everneur
Pulmonary/upper respiratory, patients, serious adverse event	table5_onerecsae.everpulm
Renal/genitourinary, patients, serious adverse event	table5_onerecsae.everrena
Sexual, patients, serious adverse event	table5_onerecsae.eversexu
Other, patients, serious adverse event	table5_onerecsae.everothe
	table5_onerecsae.everaudi, table5_onerecsae.everalle, table5_onerecsae.everocul, table5_onerecsae.everhepa, table5_onerecsae.everinfe, table5_onerecsae.evercons, table5_onerecsae.everpsyc, table5_onerecsae.evercard, table5_onerecsae.everderm, table5_onerecsae.everendo, table5_onerecsae.evergast, table5_onerecsae.evermusc, table5_onerecsae.everlymp, table5_onerecsae.everneur, table5_onerecsae.everpulm, table5_onerecsae.everrena, table5_onerecsae.eversexu, table5_onerecsae.everothe
Total, patients, serious adverse event	table5_onerecsae.everothe
Treatment	table5_all.tx, table5_onerec.tx, table5_onerecsae.tx

Table J: Comparison of values computed in integrity check to reference article Table 5 values

All adverse events

Body system/category	CBDR (N=88), Events, n Manuscript	CBDR (N=88), Events, n DSIC	Diff. (N=0)	CBDR (N=88), Patients, n Manuscript	CBDR (N=88), Patients, n DSIC	Diff. (N=0)
Auditory	6	6	0	5	5	0
Allergy	5	5	0	5	5	0
Ocular/visual	1	1	0	1	1	0
Hepatobiliary/pancreas	3	3	0	3	3	0
Infection	12	12	0	10	10	0
Constitutional symptoms	4	4	0	4	4	0
Psychiatric	6	6	0	5	5	0
Cardiovascular	3	3	0	3	3	0
Dermatological	18	18	0	12	12	0
Endocrine	5	5	0	4	4	0
Gastrointestinal	48	48	0	34	34	0
Lymphatic	0	0	0	0	0	0
Musculoskeletal/soft tissue	15	15	0	12	12	0
Neurology	14	14	0	13	13	0
Pulmonary/upper respiratory	24	24	0	16	16	0
Renal/genitourinary	3	3	0	3	3	0
Sexual	2	2	0	2	2	0
Other	10	10	0	9	9	0
Total	179	179	0	62	62	0

Body system/category	Placebo (N=81), Events, n Manuscript	Placebo (N=81), Events, n DSIC	Diff. (N=0)	Placebo (N=81), Patients, n Manuscript	Placebo (N=81), Patients, n DSIC	Diff. (N=0)
Auditory	6	6	0	5	5	0
Allergy	6	6	0	6	6	0
Ocular/visual	3	3	0	3	3	0
Hepatobiliary/pancreas	0	0	0	0	0	0
Infection	12	12	0	10	10	0

Body system/category	Placebo (N=81), Events, n Manuscript	Placebo (N=81), Events, n DSIC	Diff. (N=0)	Placebo (N=81), Patients, n Manuscript	Placebo (N=81), Patients, n DSIC	Diff. (N=0)
Constitutional symptoms	2	2	0	2	2	0
Psychiatric	4	4	0	4	4	0
Cardiovascular	3	3	0	3	3	0
Dermatological	14	14	0	10	10	0
Endocrine	3	3	0	3	3	0
Gastrointestinal	52	52	0	33	33	0
Lymphatic	0	0	0	0	0	0
Musculoskeletal/soft tissue	9	9	0	8	8	0
Neurology	10	10	0	9	9	0
Pulmonary/upper respiratory	31	31	0	18	18	0
Renal/genitourinary	2	2	0	2	2	0
Sexual	1	1	0	1	1	0
Other	16	16	0	13	13	0
Total	174	174	0	54	54	0

Serious adverse events

Body system/category	CBDR (N=88), Events, n Manuscript	CBDR (N=88), Events, n DSIC	Diff. (N=0)	CBDR (N=88), Patients, n Manuscript	CBDR (N=88), Patients, n DSIC	Diff. (N=0)
Auditory	0	0	0	0	0	0
Allergy	0	0	0	0	0	0
Ocular/visual	0	0	0	0	0	0
Hepatobiliary/pancreas	1	1	0	1	1	0
Infection	0	0	0	0	0	0
Constitutional symptoms	0	0	0	0	0	0
Psychiatric	2	2	0	2	2	0
Cardiovascular	0	0	0	0	0	0
Dermatological	0	0	0	0	0	0
Endocrine	1	1	0	1	1	0
Gastrointestinal	3	3	0	2	2	0
Lymphatic	0	0	0	0	0	0
Musculoskeletal/soft tissue	0	0	0	0	0	0
Neurology	1	1	0	1	1	0
Pulmonary/upper respiratory	0	0	0	0	0	0
Renal/genitourinary	0	0	0	0	0	0
Sexual	0	0	0	0	0	0
Other	0	0	0	0	0	0
Total	8	8	0	5	5	0

Body system/category	Placebo (N=81), Events, n Manuscript	Placebo (N=81), Events, n DSIC	Diff. (N=0)	Placebo (N=81), Patients, n Manuscript	Placebo (N=81), Patients, n DSIC	Diff. (N=0)
Auditory	0	0	0	0	0	0
Allergy	0	0	0	0	0	0
Ocular/visual	0	0	0	0	0	0
Hepatobiliary/pancreas	0	0	0	0	0	0
Infection	1	1	0	1	1	0

Body system/category	Placebo (N=81), Events, n Manuscript	Placebo (N=81), Events, n DSIC	Diff. (N=0)	Placebo (N=81), Patients, n Manuscript	Placebo (N=81), Patients, n DSIC	Diff. (N=0)
Constitutional symptoms	0	0	0	0	0	0
Psychiatric	1	1	0	1	1	0
Cardiovascular	0	0	0	0	0	0
Dermatological	0	0	0	0	0	0
Endocrine	1	1	0	1	1	0
Gastrointestinal	1	1	0	1	1	0
Lymphatic	0	0	0	0	0	0
Musculoskeletal/soft tissue	1	1	0	1	1	0
Neurology	0	0	0	0	0	0
Pulmonary/upper respiratory	0	0	0	0	0	0
Renal/genitourinary	0	0	0	0	0	0
Sexual	0	0	0	0	0	0
Other	0	0	0	0	0	0
Total	5	5	0	4	4	0

Appendix A: SAS Code

```
*** CyNCh DSIC;
*** Programmer: Allyson Mateja;
*** Date: 4/19/17;

proc format;
  value yesnof 0 = 'No'
              1 = 'Yes';
  value genderf 1 = 'Male'
               2 = 'Female';
  value weightf 1 = '<= 65 kg'
               2 = '>65 to 80 kg'
               3 = '>80 kg';
  value $steatf '0' = 'No'
               '1a' = 'Borderline zone 3 pattern'
               '1b' = 'Borderline zone 1 pattern'
               '2' = 'Definite';
  value $racef 'AmInd' = 'American Indian/Alaska Native'
              'Asian' = 'Asian'
              'Black' = 'Black or African American'
              'White' = 'White'
              'Multi' = 'More than 1 race'
              'Ref' = 'Refusal/not stated';
  value groupf 0 = 'Placebo'
               1 = 'CBDR';
  value wtf 0 = '<= 65 kg at baseline'
            1 = '>65 kg at baseline';

libname sas_data '/prj/niddk/ims_analysis/CyNCh/private_created_data/SAS_DATA/';

data table1;
  set sas_data.table1;

proc contents data = table1;

proc freq data = table1;
  tables tx;
  title 'Table 1 - TX';

proc sort data = table1;
  by tx;

proc freq data = table1;
  tables wt_strat;
  format wt_strat weightf.;
  by tx;
  title 'Table 1 - Weight stratum';

proc freq data = table1;
  tables wt_strat;
  format wt_strat weightf.;

proc means data = table1 n mean std;
```

```

var age;
class tx;
types () tx;
title 'Table 1 - Age';

proc freq data = table1;
tables gender;
format gender genderf.;
by tx;
title 'Table 1 - Gender';

proc freq data = table1;
tables gender;
format gender genderf.;

proc freq data = table1;
tables race;
format race $racef.;
by tx;
title 'Table 1 - Race';

proc freq data = table1;
tables race;
format race $racef.;

proc freq data = table1;
tables hispanic;
format hispanic yesnof.;
by tx;
title 'Table 1 - Hispanic ethnicity';

proc freq data = table1;
tables hispanic;
format hispanic yesnof.;

proc means data = table1 n mean std;
var cphys;
class tx;
types () tx;
title 'Table 1 - Self-reported pediatric QOL Physical health';

proc means data = table1 n mean std;
var csoc;
class tx;
types () tx;
title 'Table 1 - Self-reported pediatric QOL Psychosocial health';

proc means data = table1 n mean std;
var pphys;
class tx;
types () tx;
title 'Table 1 - Parent/guardian-reported pediatric QOL Physical health';

proc means data = table1 n mean std;
var psoc;
class tx;

```

```

types () tx;
title 'Table 1 - Parent/guardian-reported pediatric QOL Psychosocial health';

proc means data = table1 n median p25 p75 mean std;
var alt;
class tx;
types () tx;
title 'Table 1 - Alanine aminotransferase';

proc means data = table1 n median p25 p75 mean std;
var ast;
class tx;
types () tx;
title 'Table 1 - Aspartate aminotransferase';

proc means data = table1 n mean std;
var alkphos;
class tx;
types () tx;
title 'Table 1 - Alkaline phosphatase';

proc means data = table1 n mean std;
var ggt;
class tx;
types () tx;
title 'Table 1 - GGT';

proc means data = table1 n mean std;
var bilitot;
class tx;
types () tx;
title 'Table 1 - Total bilirubin';

proc means data = table1 n mean std;
var totchol;
class tx;
types () tx;
title 'Table 1 - Total cholesterol';

proc means data = table1 n mean std;
var hdl;
class tx;
types () tx;
title 'Table 1 - HDL cholesterol';

proc means data = table1 n mean std;
var ldl;
class tx;
types () tx;
title 'Table 1 - LDL cholesterol';

proc means data = table1 n mean std;
var nonhdlc;
class tx;
types () tx;
title 'Table 1 - Non-HDL cholesterol';

```

```

proc means data = table1 n mean std;
  var triglyc;
  class tx;
  types () tx;
  title 'Table 1 - Triglycerides';

proc means data = table1 n mean std;
  var wtkg;
  class tx;
  types () tx;
  title 'Table 1 - Weight';

proc means data = table1 n mean std;
  var bmi;
  class tx;
  types () tx;
  title 'Table 1 - BMI';

proc means data = table1 n mean std;
  var bmiz;
  class tx;
  types () tx;
  title 'Table 1 - BMI z-score';

proc means data = table1 n mean std;
  var waistcm;
  class tx;
  types () tx;
  title 'Table 1 - Waist circumference';

proc means data = table1 n mean std;
  var glucose;
  class tx;
  types () tx;
  title 'Table 1 - Fasting serum glucose';

proc means data = table1 n mean std;
  var insulin;
  class tx;
  types () tx;
  title 'Table 1 - Insulin';

proc means data = table1 n mean std;
  var homa;
  class tx;
  types () tx;
  title 'Table 1 - HOMA-IR';

proc means data = table1 n mean std;
  var systolic;
  class tx;
  types () tx;
  title 'Table 1 - Systolic blood pressure';

proc means data = table1 n mean std;

```

```

var diastoli;
class tx;
types () tx;
title 'Table 1 - Diastolic blood pressure';

proc freq data = table1;
tables diabetes;
format diabetes yesnof.;
by tx;
title 'Table 1 - Diabetes';

proc freq data = table1;
tables diabetes;
format diabetes yesnof.;

proc freq data = table1;
tables hyperten;
format hyperten yesnof.;
by tx;
title 'Table 1 - Hypertension';

proc freq data = table1;
tables hyperten;
format hyperten yesnof.;

proc freq data = table1;
tables hyperlip;
format hyperlip yesnof.;
by tx;
title 'Table 1 - Hyperlipidemia';

proc freq data = table1;
tables hyperlip;
format hyperlip yesnof.;

proc means data = table1 n mean std;
var bnas;
class tx;
types () tx;
title 'Table 1 - NAFLD Activity score';

proc means data = table1 n mean std;
var bsteato;
class tx;
types () tx;
title 'Table 1 - Steatosis score';

proc means data = table1 n mean std;
var blobinf;
class tx;
types () tx;
title 'Table 1 - Lobular inflammation score';

proc means data = table1 n mean std;
var bball;
class tx;

```

```

types () tx;
title 'Table 1 - Hepatocellular ballooning score';

proc means data = table1 n mean std;
var bportinf;
class tx;
types () tx;
title 'Table 1 - Portal inflammation score';

proc freq data = table1;
tables bfib;
by tx;
title 'Table 1 - Fibrosis stage';

proc freq data = table1;
tables bfib;

proc means data = table1 n mean std;
var bfibro;
class tx;
types () tx;
title 'Table 1 - Fibrosis stage';

proc freq data = table1;
tables bstdiag;
format bstdiag $steatf.;
by tx;
title 'Table 1 - Steatohepatitis';

proc freq data = table1;
tables bstdiag;
format bstdiag $steatf.;

data table2;
set sas_data.table2;

proc contents data=table2;

data table2;
set table2;
change_nafld_activity = fnas-bnas;
change_steatosis = fsteato-bsteato;
change_lob_infl = flobinf-blobinf;
change_hep_balloon = fball-bball;
change_portal_inf = fportinf-bportinf;
change_fibrosis = ffib-bfib;

proc sort data = table2;
by descending cyst;

proc freq data = table2;
tables improve2;
by descending cyst;
format cyst groupf. improve2 yesnof.;
title 'Table 2 - Histologic improvement: primary outcome';

```

```

proc freq data = table2;
  tables improve;
  by descending cyst;
  format cyst groupf. improve yesnof.;
  title 'Table 2 - Histologic improvement: completed follow-up evaluation';

proc means data = table2 n mean std;
  var change_naflc_activity;
  class cyst;
  format cyst groupf.;
  title 'Table 2 - Change in NAFLD activity score';

proc freq data = table2;
  tables impstea0;
  by descending cyst;
  format cyst groupf. impstea0 yesnof.;
  title 'Table 2 - Steatosis patients with improvement';

proc means data = table2 n mean std;
  var change_steatosis;
  class cyst;
  format cyst groupf.;
  title 'Table 2 - Change in Steatosis score';

proc freq data = table2;
  tables implobi0;
  by descending cyst;
  format cyst groupf. implobi0 yesnof.;
  title 'Table 2 - Lobular inflammation patients with improvement';

proc means data = table2 n mean std;
  var change_lob_infl;
  class cyst;
  format cyst groupf.;
  title 'Table 2 - Change in lobular inflammation score';

proc freq data = table2;
  tables impball2;
  by descending cyst;
  format cyst groupf. impball2 yesnof.;
  title 'Table 2 - Hepatocellular ballooning patients with improvement';

proc means data = table2 n mean std;
  var change_hep_balloon;
  class cyst;
  format cyst groupf.;
  title 'Table 2 - Change in hepatocellular ballooning score';

proc freq data = table2;
  tables impport0;
  by descending cyst;
  format cyst groupf. impport0 yesnof.;
  title 'Table 2 - Portal inflammation patients with improvement';

proc means data = table2 n mean std;
  var change_portal_inf;

```

```

class cyst;
format cyst groupf.;
title 'Table 2 - Change in portal inflammation score';

proc freq data = table2;
tables impfib2;
by descending cyst;
format cyst groupf. impfib2 yesnof.;
title 'Table 2 - Fibrosis patients with improvement';

proc means data = table2 n mean std;
var change_fibrosis;
class cyst;
format cyst groupf.;
title 'Table 2 - Change in Fibrosis score';

proc freq data = table2;
tables resolve2;
by descending cyst;
format cyst groupf. resolve2 yesnof.;
title 'Table 2 - Resolution of NASH';

data table3;
set sas_data.table3;

proc contents data = table3;

proc freq data = table3;
tables tx;
where (alt_d ne . or ast_d ne . or alkphos1 ne . or ggt_d ne . or totcholl ne . or hdl_d ne . or ldl_d ne . or nonhdlc1 ne . or triglyc1 ne . or wtkg_d
ne . or bmi_d ne . or bmiz_d ne . or
waistcml ne . or glucosel ne . or homa_d ne . or systol1l ne . or diastoll ne . or csoc_d ne . or cphys_d ne . or pphys_d ne . or psoc_d ne .);

proc means data = table3 n mean std;
var alt_d;
class tx;
title 'Table 3 - ALT change';

proc means data = table3 n mean std;
var ast_d;
class tx;
title 'Table 3 - AST change';

proc means data = table3 n mean std;
var alkphos1;
class tx;
title 'Table 3 - Alkaline phosphatase change';

proc means data = table3 n mean std;
var ggt_d;
class tx;
title 'Table 3 - GGT change';

proc means data = table3 n mean std;
var totcholl;
class tx;

```



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    title 'Table 3 - Total cholesterol change';

proc means data = table3 n mean std;
  var hdl_d;
  class tx;
  title 'Table 3 - HDL change';

proc means data = table3 n mean std;
  var ldl_d;
  class tx;
  title 'Table 3 - LDL change';

proc means data = table3 n mean std;
  var nonhdlc1;
  class tx;
  title 'Table 3 - Non-HDL cholesterol change';

proc means data = table3 n mean std;
  var triglyc1;
  class tx;
  title 'Table 3 - Triglycerides change';

proc means data = table3 n mean std;
  var wtkg_d;
  class tx;
  title 'Table 3 - Weight change';

proc means data = table3 n mean std;
  var bmi_d;
  class tx;
  title 'Table 3 - BMI change';

proc means data = table3 n mean std;
  var bmiz_d;
  class tx;
  title 'Table 3 - BMI z-score change';

proc means data = table3 n mean std;
  var waistcml;
  class tx;
  title 'Table 3 - Waist circumference change';

proc means data = table3 n mean std;
  var glucosel;
  class tx;
  title 'Table 3 - Glucose change';

proc means data = table3 n mean std;
  var insulin1;
  class tx;
  title 'Table 3 - Insulin change';

proc means data = table3 n mean std;
  var homa_d;
  class tx;
  title 'Table 3 - HOMA-IR change';

```

```

proc means data = table3 n mean std;
  var systol1;
  class tx;
  title 'Table 3 - Systolic blood pressure change';

proc means data = table3 n mean std;
  var diastoll;
  class tx;
  title 'Table 3 - Diastolic blood pressure change';

proc means data = table3 n mean std;
  var cphys_d;
  class tx;
  title 'Table 3 - Self-reported QOL Physical health change';

proc means data = table3 n mean std;
  var csoc_d;
  class tx;
  title 'Table 3 - Self-reported QOL Psychosocial health change';

proc means data = table3 n mean std;
  var pphys_d;
  class tx;
  title 'Table 3 - Parent/guardian-reported QOL Physical health change';

proc means data = table3 n mean std;
  var psoc_d;
  class tx;
  title 'Table 3 - Parent/guardian-reported QOL Psychosocial health change';

data table4;
  set sas_data.table4;

proc contents data=table4;

proc sort data = table4;
  by wt_bin tx;

proc freq data = table4;
  tables improve2;
  by wt_bin tx;
  format wt_bin wtf. improve2 yesnof.;
  title 'Table 4 - Histologic improvement: primary outcome';

proc freq data = table4;
  tables improve;
  by wt_bin tx;
  format wt_bin wtf. improve yesnof.;
  title 'Table 4 - Histologic improvement: completed follow-up evaluation';

proc freq data = table4;
  tables improve2;
  by wt_bin tx;
  format wt_bin wtf. improve2 yesnof.;
  where adherent=1;

```

```

title 'Table 4 - Adherent to prescribed dose of medication';

proc means data = table4 n mean std;
  var dnas;
  class wt_bin tx;
  format wt_bin wtf.;
  title 'Table 4 - Change in NAFLD activity score';

proc freq data = table4;
  tables impsteat;
  by wt_bin tx;
  format wt_bin wtf. impsteat yesnof.;
  title 'Table 4 - Steatosis patients with improvement';

proc means data = table4 n mean std;
  var dsteato;
  class wt_bin tx;
  format wt_bin wtf.;
  title 'Table 4 - Change in Steatosis score';

proc freq data = table4;
  tables implobin;
  by wt_bin tx;
  format wt_bin wtf. implobin yesnof.;
  title 'Table 4 - Lobular inflammation patients with improvement';

proc means data = table4 n mean std;
  var dlobinf;
  class wt_bin tx;
  format wt_bin wtf.;
  title 'Table 4 - Change in lobular inflammation score';

proc freq data = table4;
  tables impball2;
  by wt_bin tx;
  format wt_bin wtf. impball2 yesnof.;
  title 'Table 4 - Hepatocellular ballooning patients with improvement';

proc means data = table4 n mean std;
  var dball;
  class wt_bin tx;
  format wt_bin wtf.;
  title 'Table 4 - Change in hepatocellular ballooning score';

proc freq data = table4;
  tables impporti;
  by wt_bin tx;
  format wt_bin wtf. impporti yesnof.;
  title 'Table 4 - Portal inflammation patients with improvement';

proc means data = table4 n mean std;
  var dportinf;
  class wt_bin tx;
  format wt_bin wtf.;
  title 'Table 4 - Change in portal inflammation score';

```

```

proc freq data = table4;
  tables impfib2;
  by wt_bin tx;
  format wt_bin wtf. impfib2 yesnof.;
  title 'Table 4 - Fibrosis patients with improvement';

proc means data = table4 n mean std;
  var dfib;
  class wt_bin tx;
  format wt_bin wtf.;
  title 'Table 4 - Change in Fibrosis score';

proc means data = table4 n mean std;
  var alt_d;
  class wt_bin tx;
  format wt_bin wtf.;
  title 'Table 4 - Change in ALT';

proc means data = table4 n mean std;
  var ast_d;
  class wt_bin tx;
  format wt_bin wtf.;
  title 'Table 4 - Change in AST';

proc means data = table4 n mean std;
  var bmiz_d;
  class wt_bin tx;
  format wt_bin wtf.;
  title 'Table 4 - Change in BMI z-score';

data table5_all;
  set sas_data.table5_all;

data table5_onerec;
  set sas_data.table5_onerec;

data table5_onerecsae;
  set sas_data.table5_onerecsae;

proc contents data = table5_all;
proc contents data = table5_onerec;
proc contents data = table5_onerecsae;

data table5_all;
  set table5_all;
  total = sum(auditory, allergy, ocular, hepatobi, infectio, constitu, psychiat, cardiova, dermatol, endocrin, gastroin, lymphati, musculos, neurolog,
  pulmonar, renal, sexual, othersys);

proc sort data = table5_all;
  by id;

proc sort data = table1;
  by id;

data table5_all;
  merge table5_all (in=val1 drop=tx)

```

```

        table1      (in=val2 keep=id tx);
    by id;
    if vall and val2 then output;

proc sort data = table5_all;
    by tx;

proc freq data = table5_all;
    tables auditory allergy ocular hepatobi infectio constitu psychiat cardiova dermatol endocrin gastroin lymphati musculos neurolog      pulmonar renal
sexual othersys;
    format auditory allergy ocular hepatobi infectio constitu psychiat cardiova dermatol endocrin gastroin lymphati musculos neurolog      pulmonar renal
sexual othersys yesnof.;
    by tx;
    title 'Table 5 - All adverse events, events';

proc means data = table5_all sum;
    var total;
    class tx;
    title 'Table 5 - All adverse events total';

proc freq data = table5_all;
    tables auditory allergy ocular hepatobi infectio constitu psychiat cardiova dermatol endocrin gastroin lymphati musculos neurolog      pulmonar renal
sexual othersys;
    format auditory allergy ocular hepatobi infectio constitu psychiat cardiova dermatol endocrin gastroin lymphati musculos neurolog      pulmonar renal
sexual othersys yesnof.;
    by tx;
    where sae=1;
    title 'Table 5 - Serious adverse events, events';

proc means data = table5_all sum;
    var total;
    class tx;
    where sae=1;
    title 'Table 5 - Serious adverse events total';

proc sort data = table5_onerec;
    by id;

data table5_onerec;
    merge table5_onerec (in=vall drop=tx)
          table1      (in=val2 keep=id tx);
    by id;
    if vall and val2 then output;

proc sort data = table5_onerec;
    by tx;

proc freq data = table5_onerec;
    tables everaudi everalle everocul everhepa everinfe evercons everpsyc evercard everderm everendo evergast everlymp evermusc everneur everpulm everrena
eversexu everothe;
    format everaudi everalle everocul everhepa everinfe evercons everpsyc evercard everderm everendo evergast everlymp evermusc everneur everpulm everrena
eversexu everothe yesnof.;
    by tx;
    title 'Table 5 - All adverse events, patients';

proc freq data = table5_onerec;

```

```

    tables tx;
    where (everaudi=1 or everalle=1 or everocul=1 or everhepa=1 or everinfe=1 or evercons=1 or everpsyc=1 or evercard=1 or everderm=1 or everendo=1 or
evergast=1 or everlymp=1 or
        evermusc=1 or everneur=1 or everpulm=1 or everrena=1 or eversexu=1 or everothe=1);
    title 'Table 5 - Total, All adverse events, patients';

proc sort data = table5_onerecsae;
    by id;

data table5_onerecsae;
    merge table5_onerecsae (in=val1 drop=tx)
          table1           (in=val2 keep=id tx);
    by id;
    if val1 and val2 then output;

proc sort data = table5_onerecsae;
    by tx;

proc freq data = table5_onerecsae;
    tables everaudi everalle everocul everhepa everinfe evercons everpsyc evercard everderm everendo evergast everlymp evermusc everneur everpulm everrena
eversexu everothe;
    format everaudi everalle everocul everhepa everinfe evercons everpsyc evercard everderm everendo evergast everlymp evermusc everneur everpulm everrena
eversexu everothe yesnof.;
    by tx;
    title 'Table 5 - Serious adverse events, patients';

proc freq data = table5_onerecsae;
    tables tx;
    where (everaudi=1 or everalle=1 or everocul=1 or everhepa=1 or everinfe=1 or evercons=1 or everpsyc=1 or evercard=1 or everderm=1 or everendo=1 or
evergast=1 or everlymp=1 or
        evermusc=1 or everneur=1 or everpulm=1 or everrena=1 or eversexu=1 or everothe=1);
    title 'Table 5 - Total, Serious adverse events, patients';

```