

Leronlimab a Humanized Anti-CCR5 Monoclonal Antibody Ameliorates Hepatic Fibrosis in Two Preclinical Fibrosis Mouse Models

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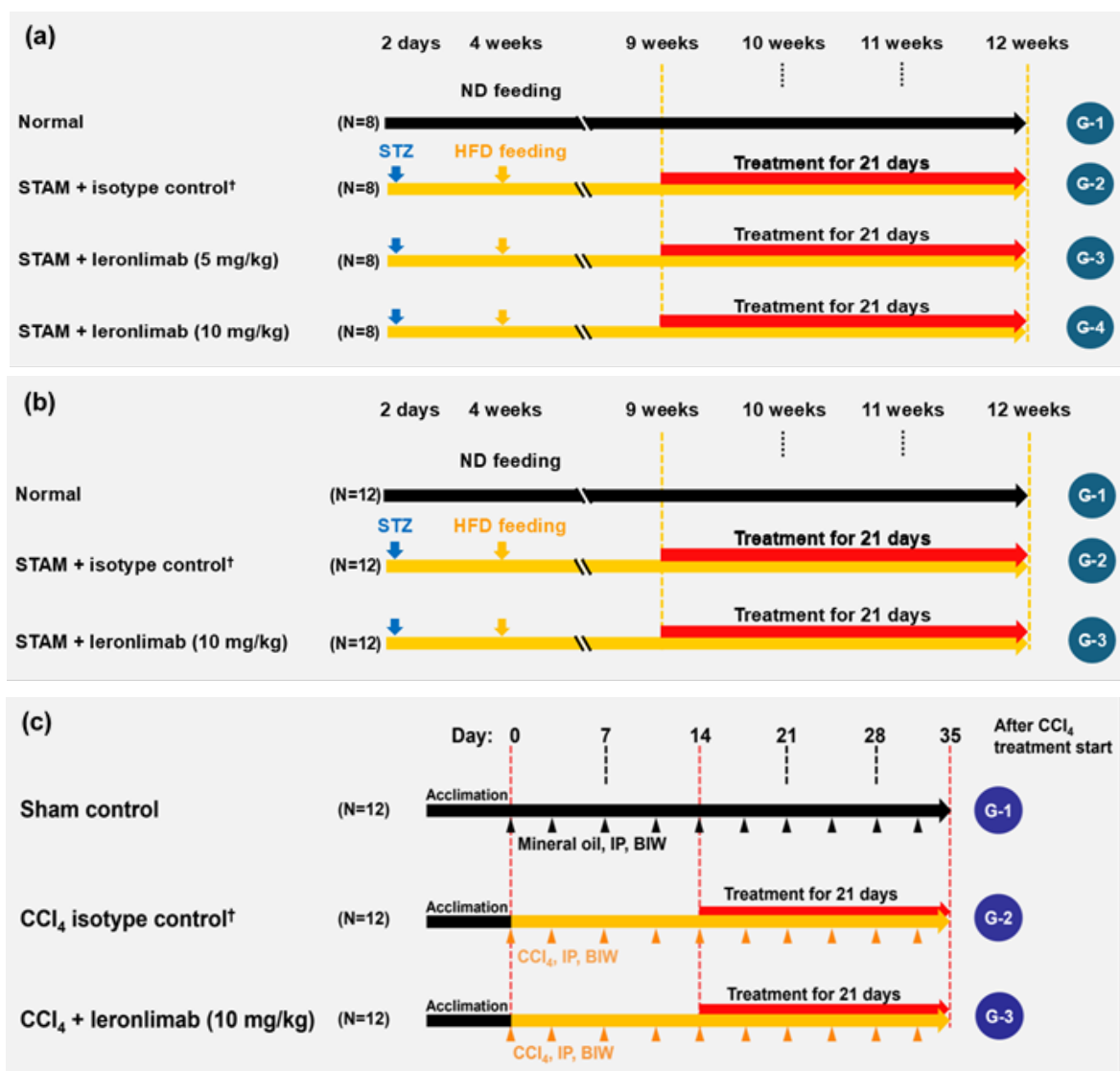


Figure S1: STAM models 1 and 2 and CCl₄-induced fibrosis model trial designs. Schematic design of the three animal models. Panel A) STAM models 1 trial design; Panel B) STAM models 2 trial design; Panel C) CCl₄-induced fibrosis model trial design. Note: †Ultra-LEAF purified human IgG4 isotype control recombinant antibody. BIW=Twice per week; CCl₄=Carbon Tetrachloride; HFD=High Fat Diet; IP=Intra Peritoneal; ND=Normal Diet; STAM=Stelic Animal Model; STZ=Streptozotocin.

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Table S1: Test item, lot number and storage conditions.

Test item/vehicle	Lot number and storage conditions
Leronlimab Final Drug Product (FDP), 175 mg/mL	Manufacturer: Samsung BioLogics Co., Ltd.
	Material specifications number: SPEC-0008 (Rev. 01) Item/part number: PC2AA (SBL)
	Lot number: 2100416
	Storage: 2-8°C
Formulation buffer for dilution (placebo to match leronlimab)	Manufacturer: Samsung BioLogics Co., Ltd.
	Material specifications number: SPEC-0009 (Rev. 00) Item/part number: PC2B (SBL)
	Lot number: 2100540
	Storage: 2-8°C
Ultra-Low Endotoxin Azide-Free (LEAF) purified human IgG4 Isotype control recombinant antibody (Isotype control)	Manufacturer: BioLegend
	Other names: IGHG4, immunoglobulin heavy chain constant region gamma 4
	Isotype: Human IgG4 antibody type: Recombinant host species: Human
	Formulation: 0.2 µm filtered in phosphate-buffered solution, pH 7.2, containing no preservative Lot number: B425679 Storage: 2-8°C

Table S2: Definition of NAFLD Activity Score (NAS) components.

Item	Extent	Score
Steatosis	Steatosis at 50-fold magnification	
	<5%	0
	5-33%	1
	>33-66%	2
	>66%	3
Lobular inflammation	Estimation of inflammatory foci	
	No foci	0
	<2 foci/200x	1
	2-4 foci/200x	2
	>4 foci/200x	3
Ballooning	Estimation of number of ballooning cells	
	None	0
	Few ballooning cells	1
	Many cells/prominent ballooning	2

Table S3: STAM model 1 individual data.

Group	Mouse ID	Body weight (g)	Liver weight (mg)	Liver-to-body weight ratio (%)	Whole blood glucose (mg/dL)	Plasma ALT (U/L)	Plasma AST (U/L)	Plasma triglyceride (mg/dL)	Triglyceride (mg/g liver)	Steatosis	Inflammation	Ballooning	NAS	Sirius red-positive area (%)	Oil red-positive area (%)
Normal	101	28.5	1416	5.0	159	19	53	89	4.0	0	0	0	0	0.32	3.49
	102	28.2	1326	4.7	183	18	39	73	5.9	0	0	0	0	0.41	1.32
	103	27.6	1257	4.6	207	24	43	88	7.5	0	0	0	0	0.22	1.60
	104	26.8	1290	4.8	192	19	46	172	5.3	0	0	0	0	0.28	2.48
	105	29.0	1403	4.8	181	20	35	165	4.6	0	0	0	0	0.11	1.29
	106	26.9	1129	4.2	213	20	73	124	4.9	0	0	0	0	0.43	2.15
	107	26.5	1192	4.5	240	19	34	78	1.6	0	0	0	0	0.44	1.32
	108	26.9	1200	4.5	175	16	39	129	5.8	0	0	0	0	0.28	2.81

	201	25.2	1815	7.2	522	26	75	116	18.3	1	2	2	5	0.82	28.38
	202														
Isotype control	203	12.7	1248	9.8	476	30	168	3195	24.3	1	3	0	4	1.01	19.20
	204	15.9	1299	8.2	775	126	254	3027	36.3	2	3	0	5	0.73	19.78
	205	23.8	1752	7.4	609	29	67	835	16.8	0	3	1	4	0.96	22.51
	206	17.8	1931	10.8	520	30	60	4559	26.3	2	2	0	4	1.20	23.95
	207	21.1	1679	8.0	701	26	73	1581	11.2	1	2	2	5	1.02	25.06
	208	21.0	1521	7.2	594	44	93	243	14.2	1	3	1	5	0.97	24.72
	301	25.2	1768	7.0	549	35	87	573	32.2	0	2	0	2	1.10	26.12
	302	18.3	1755	9.6	426	24	57	1052	90.7	1	2	0	3	0.80	19.96
Leronlimab low	303	24.0	1679	7.0	562	26	66	124	38.0	1	2	0	3	0.38	24.08
	304	21.6	1708	7.9	754	25	56	518	35.8	1	2	0	3	0.95	27.87
	305	21.7	1737	8.0	514	33	59	610	31.3	1	2	0	3	0.50	31.20
	306	22.1	1672	7.6	787	24	65	906	22.4	0	1	1	2	0.70	20.18
	307	22.4	1878	8.4	645	21	62	987	38.0	1	2	2	5	0.99	34.40
	308	17.5	1569	9.0	>900	41	159	452	33.1	1	3	0	4	0.65	41.80
	401	23.2	1921	8.3	526	26	55	3317	31.7	1	1	0	2	0.63	21.29
	402	24.9	1674	6.7	682	30	73	62	57.3	0	1	1	2	0.60	35.06
Leronlimab high	403	13.9	1486	10.7	414	38	135	5982	75.1	1	3	0	4	0.42	16.59
	404	22.4	1577	7.0	562	29	62	955	33.7	0	2	0	2	0.78	32.66
	405	25.3	1956	7.7	549	46	99	482	58.4	0	3	0	3	0.44	31.76
	406	21.0	1638	7.8	595	24	51	601	18.9	1	2	2	5	0.55	20.59
	407	22.6	1795	7.9	479	44	81	435	50.6	1	2	0	3	0.47	35.25
	408	20.9	1580	7.6	575	32	69	176	30.0	1	2	0	3	0.71	28.34

Note: / : Dead

Table S4: STAM model 2 individual data.

Group	Mouse ID	Body weight (g)	Liver weight (mg)	Liver-to-body weight ratio (%)	Whole blood glucose (mg/dL)	Plasma ALT (U/L)	Plasma AST (U/L)	Plasma triglyceride (mg/dL)	Triglyceride (mg/g liver)	Steatosis	Inflammation	Ballooning	NAS	Sirius red-positive area (%)	Oil red-positive area (%)
Normal	101	24.8	1206	4.9	176	18	44	107	4.4	0	0	0	0	0.26	0.07
	102	24.2	1195	4.9	226	20	61	96	2.5	0	0	0	0	0.37	0.03
	103	23.7	1016	4.3	190	20	70	45	2.4	0	0	0	0	0.43	0.25
	104	24.2	1031	4.3	220	20	37	86	3.7	0	0	0	0	0.30	0.05
	105	25.0	1209	4.8	185	28	261	98	3.3	0	0	0	0	0.36	0.08
	106	24.0	1181	4.9	181	18	40	151	2.6	0	0	0	0	0.41	0.15
	107	24.8	1245	5.0	179	17	74	195	5.5	0	0	0	0	0.32	0.17
	108	25.2	1182	4.7	208	20	60	94	4.8	0	0	0	0	0.45	0.14
	109	24.8	1080	4.4	176	18	37	112	4.8	0	0	0	0	0.41	0.08
	110	25.1	1087	4.3	179	19	46	75	8.3	0	0	0	0	0.44	0.27
	111	23.3	811	3.5	182	21	102	47	6.2	0	0	0	0	0.40	0.21
	112	24.1	1066	4.4	189	19	38	115	2.8	0	0	0	0	0.39	0.06

	201	25.0	1846	7.4	585	44	107	439	32.7	1	2	2	5	1.04	30.44	
	202	24.7	2013	8.1	559	57	116	1489	42.0	1	2	1	4	1.14	17.65	
	203	[Redacted]														
	204	/														
Isotype control	205	25.6	1563	6.1	545	46	80	2033	27.1	0	2	2	4	1.29	13.64	
	206	21.5	1391	6.5	636	35	73	147	21.6	1	2	2	5	1.45	13.31	
	207	[Redacted]														
	208	19.4	1592	8.2	456	47	117	1388	38.1	1	3	1	5	1.52	25.87	
	209	25.7	1949	7.6	412	47	99	1240	46.4	1	3	1	5	1.27	31.31	
	210	20.7	1953	9.4	446	43	87	2000	32.0	1	3	0	4	1.29	26.84	
	211	23.4	1605	6.9	543	50	103	121	42.4	1	2	2	5	1.46	11.46	
	212	18.5	1434	7.8	520	40	79	1126	37.8	1	3	1	5	1.58	23.42	
	Leronlimab	301	24.0	1922	8.0	474	92	204	1276	30.7	1	2	0	3	0.73	26.74
		302	21.7	1550	7.1	487	74	127	576	38.9	0	2	0	2	0.90	37.02
303		22.3	1606	7.2	499	57	110	1122	33.6	0	3	0	3	0.46	17.52	
304		21.3	2370	11.1	578	171	363	2297	52.7	2	3	0	5	1.02	9.36	
305		23.5	1919	8.2	486	44	74	959	38.4	1	2	0	3	0.81	36.91	
306		24.1	1546	6.4	508	145	366	683	38.2	0	3	0	3	1.07	20.57	
307		21.7	2004	9.2	501	89	157	222	41.1	0	2	0	2	0.79	17.66	
308		20.7	1927	9.3	498	53	103	2162	38.3	1	3	0	4	0.87	17.53	
309		23.9	1976	8.3	497	64	119	2413	32.7	1	3	0	4	1.10	24.82	
310		23.6	1791	7.6	506	44	100	1693	23.4	0	2	1	3	0.61	17.54	
311		23.2	1675	7.2	447	64	120	993	38.1	0	3	0	3	0.73	24.20	
312		19.2	1740	9.1	497	40	124	1132	45.1	1	3	0	4	0.98	33.72	

Note: [Redacted] Euthanasia; / : Dead

Table S5: CCl₄ model individual data.

Group	Mouse ID	Body weight (g)	Liver weight (mg)	Liver-to-body weight ratio (%)	Plasma ALT (U/L)	Plasma ALT (U/L)	Hydroxyproline (µg/mg total protein)	Sirius red-positive area (%)
Control	101	23.1	1034	4.5	14	1.58	1.58	0.74
	102	23.2	989	4.3	17	1.11	1.11	1.40
	103	23.2	1108	4.8	12	1.76	1.76	1.01
	104	20.0	926	4.6	18	2.66	2.66	0.44
	105	21.6	971	4.5	12	2.58	2.58	0.89
	106	20.6	867	4.2	15	3.06	3.06	0.71
	107	23.1	913	4.0	15	2.28	2.28	1.09
	108	21.1	945	4.5	15	2.50	2.50	0.98
	109	22.9	1039	4.5	13	2.42	2.42	0.79
	110	21.6	828	3.8	13	2.31	2.31	1.51
	111	23.0	1065	4.6	16	3.00	3.00	0.84
	112	19.9	869	4.4	12	1.75	1.75	1.75

Isotype control	201	21.8	1121	5.1	28	3.38	3.38	4.21
	202	21.8	1009	4.6	28	2.65	2.65	3.43
	203	21.8	908	4.2	22	1.72	1.72	5.38
	204	20.4	986	4.8	33	2.61	2.61	4.23
	205	21.1	1055	5.0	35	2.33	2.33	3.38
	206	18.6	862	4.6	27	3.51	3.51	3.24
	207	21.6	1111	5.1	21	2.86	2.86	4.66
	208	22.7	1079	4.8	29	2.70	2.70	3.78
	209	21.8	1120	5.1	20	2.57	2.57	4.35
	210	24.6	918	3.7	16	2.36	2.36	3.93
	211	20.5	1046	5.1	21	3.36	3.36	4.30
	212	21.3	1018	4.8	22	2.64	2.64	4.80
Leronlimab	301	21.7	1047	4.8	29	2.11	2.11	3.71
	302	20.6	1092	5.3	30	2.85	2.85	3.43
	303	20.7	1029	5.0	30	3.20	3.20	4.16
	304	20.0	780	3.9	26	2.68	2.68	3.42
	305	21.6	1077	5.0	25	2.72	2.72	2.44
	306	18.6	874	4.7	28	2.11	2.11	4.14
	307	20.9	1075	5.1	24	3.03	3.03	3.25
	308	22.0	1041	4.7	24	2.70	2.70	3.63
	309	21.2	918	4.3	29	3.49	3.49	2.25
	310	21.5	1028	4.8	24	1.81	1.81	2.73
	311	21.1	982	4.7	22	2.34	2.34	2.70
	312	21.7	1143	5.3	20	2.16	2.16	2.02

Table S6: STAM model 1 effect side and 95% confidence interval.

Body weight	Normal	Isotype control	Leronlimab low	Leronlimab high
Lower 95% CI of mean	26.78	15.55	19.43	18.80
Upper 95% CI of mean	28.32	23.74	23.77	24.75
Effect size (Cohen's d) (vs. Isotype control)	-2.61	-	-0.56	-0.55
Liver weight	Normal	Isotype control	Leronlimab low	Leronlimab high
Lower 95% CI of mean	1191	1366	1646	1561
Upper 95% CI of mean	1362	1847	1795	1846
Effect size (Cohen's d) (vs. Isotype control)	1.71	-	-0.61	-0.45
Liver-to-body weight ratio	Normal	Isotype control	Leronlimab low	Leronlimab high
Lower 95% CI of mean	4.433	7.075	7.298	6.945
Upper 95% CI of mean	4.842	9.668	8.827	8.980
Effect size (Cohen's d) (vs. Isotype control)	3.95	-	0.26	0.31
Whole blood glucose	Normal	Isotype control	Leronlimab low	Leronlimab high
Lower 95% CI of mean	172.5	500.5	508.7	481.2
Upper 95% CI of mean	215.0	698.6	775.5	614.3
Effect size (Cohen's d) (vs. Isotype control)	5.42	-	-0.30	0.56

Plasma ALT	Normal	Isotype control	Leronlimab low	Leronlimab high
Lower 95% CI of mean	17.48	10.68	22.85	26.79
Upper 95% CI of mean	21.27	78.17	34.40	40.46
Effect size (Cohen's d) (vs. Isotype control)	1.02	-	0.60	0.40
Plasma AST	Normal	Isotype control	Leronlimab low	Leronlimab high
Lower 95% CI of mean	34.56	46.09	47.28	55.08
Upper 95% CI of mean	55.94	179.60	105.50	101.20
Effect size (Cohen's d) (vs Isotype control)	1.36	-	0.67	0.66
Plasma triglyceride	Normal	Isotype control	Leronlimab low	Leronlimab high
Lower 95% CI of mean	82.27	372.00	391.90	-243.50
Upper 95% CI of mean	147.20	3501.00	913.60	3246.00
Effect size (Cohen's d) (vs. Isotype control)	1.58	-	1.10	0.23
Liver triglyceride	Normal	Isotype control	Leronlimab low	Leronlimab high
Lower 95% CI of mean	3.519	13.130	22.620	28.740
Upper 95% CI of mean	6.381	28.980	57.750	60.190
Effect size (Cohen's d) (vs. Isotype control)	2.70	-	-1.16	-1.56
NAFLD Activity score	Normal	Isotype control	Leronlimab low	Leronlimab high
Lower 95% CI of mean	0.0000	4.0770	2.2960	2.1060
Upper 95% CI of mean	0.0000	5.0660	3.9540	3.8940
Effect size (Cohen's d) (vs. Isotype control)	13.54	-	1.86	1.83
Steatosis score	Normal	Isotype control	Leronlimab low	Leronlimab high
Lower 95% CI of mean	0.0000	0.5047	0.3630	0.1923
Upper 95% CI of mean	0.0000	1.7810	1.1370	1.0580
Effect size (Cohen's d) (vs. Isotype control)	2.31	-	0.50	0.83
Inflammation score	Normal	Isotype control	Leronlimab low	Leronlimab high
Lower 95% CI of mean	0.000	2.077	1.553	1.368
Upper 95% CI of mean	0.000	3.066	2.447	2.632
Effect size (Cohen's d) (vs. Isotype control)	7.65	-	1.20	0.88
Ballooning score	Normal	Isotype control	Leronlimab low	Leronlimab high
Lower 95% CI of mean	0.000	0.025	-0.247	-0.247
Upper 95% CI of mean	0.000	1.689	0.997	0.997
Effect size (Cohen's d) (vs. Isotype control)	1.47	-	0.63	0.63
Fibrosis area	Normal	Isotype control	Leronlimab low	Leronlimab high
Lower 95% CI of mean	0.2158	0.8192	0.5506	0.4665
Upper 95% CI of mean	0.4067	1.0980	0.9669	0.6835
Effect size (Cohen's d) (vs. Isotype control)	5.00	-	0.95	2.72
Oil red-positive area	Normal	Isotype control	Leronlimab low	Leronlimab high
Lower 95% CI of mean	1.373	20.420	22.060	21.630
Upper 95% CI of mean	2.742	26.320	34.590	33.750
Effect size (Cohen's d) (vs. Isotype control)	9.47	-	-0.84	-0.75

Table S7: STAM model 2 effect side and 95% confidence interval.

Body weight	Normal	Isotype control	Leronlimab
Lower 95% CI of mean	24.05	20.60	21.45
Upper 95% CI of mean	24.82	24.85	23.42
Effect size (Cohen's d) (vs. Isotype control)	-0.92	-	0.14
Liver weight	Normal	Isotype control	Leronlimab
Lower 95% CI of mean	1032	1523	1686
Upper 95% CI of mean	1186	1888	1985
Effect size (Cohen's d) (vs. Isotype control)	3.32	-	-0.55
Liver-to-body weight ratio	Normal	Isotype control	Leronlimab
Lower 95% CI of mean	4.263	6.794	7.406
Upper 95% CI of mean	4.803	8.318	9.044
Effect size (Cohen's d) (vs. Isotype control)	4.20	-	-0.57
Whole blood glucose	Normal	Isotype control	Leronlimab
Lower 95% CI of mean	179.9	467.1	479.0
Upper 95% CI of mean	201.9	577.8	517.3
Effect size (Cohen's d) (vs. Isotype control)	6.82	-	0.46
Plasma ALT	Normal	Isotype control	Leronlimab
Lower 95% CI of mean	18.04	40.69	51.90
Upper 95% CI of mean	21.63	50.20	104.30
Effect size (Cohen's d) (vs. Isotype control)	5.62	-	-1.03
Plasma AST	Normal	Isotype control	Leronlimab
Lower 95% CI of mean	32.78	83.00	101.00
Upper 95% CI of mean	112.20	108.30	226.80
Effect size (Cohen's d) (vs. Isotype control)	0.48	-	-0.90
Plasma triglyceride	Normal	Isotype control	Leronlimab
Lower 95% CI of mean	75.54	549.80	846.00
Upper 95% CI of mean	128.00	1669.00	1742.00
Effect size (Cohen's d) (vs. Isotype control)	2.13	-	-0.26
Liver triglyceride	Normal	Isotype control	Leronlimab
Lower 95% CI of mean	3.143	29.460	32.950
Upper 95% CI of mean	5.407	41.670	42.250
Effect size (Cohen's d) (vs. Isotype control)	5.87	-	-0.27
NAFLD Activity score	Normal	Isotype control	Leronlimab
Lower 95% CI of mean	0.000	4.282	2.700
Upper 95% CI of mean	0.000	5.051	3.800
Effect size (Cohen's d) (vs. Isotype control)	14.38	-	1.93
Steatosis score	Normal	Isotype control	Leronlimab
Lower 95% CI of mean	0.0000	0.6327	0.1586
Upper 95% CI of mean	0.0000	1.1450	1.0080

Effect size (Cohen's d) (vs. Isotype control)	4.11	-	0.55
Inflammation score	Normal	Isotype control	Leronlimab
Lower 95% CI of mean	0.0000	2.0390	2.2560
Upper 95% CI of mean	0.0000	2.8500	2.9110
Effect size (Cohen's d) (vs. Isotype control)	7.15	-	-0.27
Ballooning score	Normal	Isotype control	Leronlimab
Lower 95% CI of mean	0.0000	0.7898	-0.1001
Upper 95% CI of mean	0.0000	1.8770	0.2667
Effect size (Cohen's d) (vs. Isotype control)	2.91	-	2.46
Fibrosis area	Normal	Isotype control	Leronlimab
Lower 95% CI of mean	0.3409	1.2000	0.7177
Upper 95% CI of mean	0.4158	1.4750	0.9606
Effect size (Cohen's d) (vs. Isotype control)	7.71	-	2.68
Oil red-positive area	Normal	Isotype control	Leronlimab
Lower 95% CI of mean	0.0785	15.6500	18.1200
Upper 95% CI of mean	0.1815	27.4500	29.1500
Effect size (Cohen's d) (vs. Isotype control)	4.30	-	-0.25

Table S8: CCl₄ model effect size and 95% confidence interval.

Body weight	Control	Isotype control	Leronlimab
Lower 95% CI of mean	21.12	20.60	20.37
Upper 95% CI of mean	22.77	22.40	21.56
Effect size (Cohen's d) (vs. Isotype control)	-0.30	-	0.42
Liver weight	Control	Isotype control	Leronlimab
Lower 95% CI of mean	907.50	964.20	941.70
Upper 95% CI of mean	1018.00	1075.00	1073.00
Effect size (Cohen's d) (vs. Isotype control)	0.64	-	0.13
Liver-to-body weight ratio	Control	Isotype control	Leronlimab
Lower 95% CI of mean	4.215	4.470	4.546
Upper 95% CI of mean	4.568	5.013	5.054
Effect size (Cohen's d) (vs Isotype control)	0.85	-	-0.25
Plasma ALT	Control	Isotype control	Leronlimab
Lower 95% CI of mean	13.05	21.54	23.83
Upper 95% CI of mean	15.61	28.79	28.01
Effect size (Cohen's d) (vs. Isotype control)	2.46	-	-0.21
Liver hydroxyproline	Control	Isotype control	Leronlimab
Lower 95% CI of mean	1.88	2.40	2.28
Upper 95% CI of mean	2.63	3.05	2.92
Effect size (Cohen's d) (vs. Isotype control)	0.85	-	0.24
Fibrosis area	Normal	Isotype control	Leronlimab
Lower 95% CI of mean	0.7750	3.7390	2.7000

Upper 95% CI of mean	1.2500	4.5420	3.6130
Effect size (Cohen's d) (vs. Isotype control)	6.06	-	1.45
0.3409	0.3409	0.3409	0.3409

Table S9: Differences in liver hydroxyproline content between the Isotype control group and leronlimab.

Liver hydroxyproline ($\mu\text{g/mL}$)		Bonferroni multiple comparison test (p value)	Student's t-test (two tailed p value)
Control vs. Isotype control	2.25 \pm 0.59	0.1849	0.0465
Leronlimab vs. Isotype control	2.6 \pm 0.50	>0.9999	0.5532