

SUPPLEMENTARY FILE

AN OPEN LABEL, DOSE ESCALATION STUDY TO ASSESS THE SAFETY AND EFFICACY OF IL-22 AGONIST F-652 IN PATIENTS WITH ALCOHOLIC HEPATITIS

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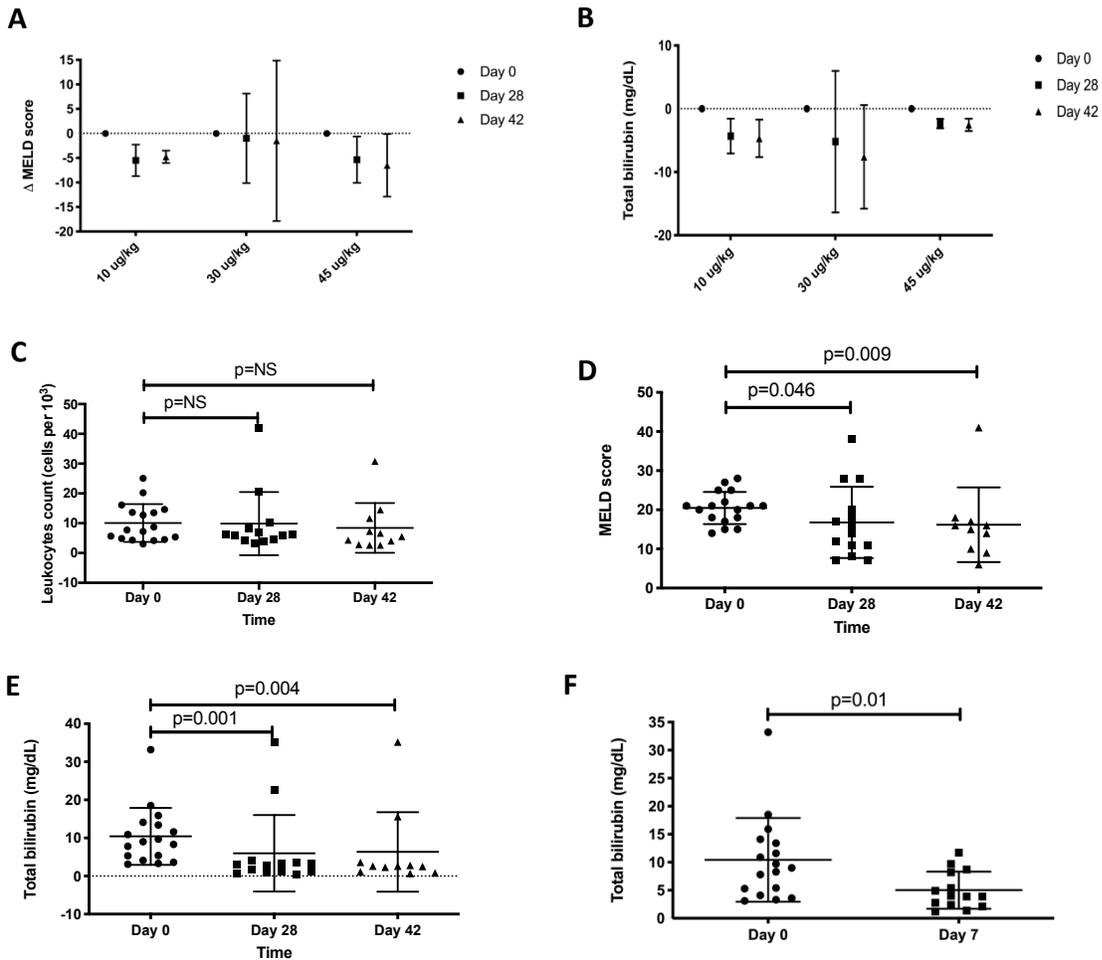
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Supplementary Figure 1

Clinical characteristics of the F-652 cohort according to dose of the administered drug at baseline, day 28 and day 42. (A) A trend in reduction of MELD score was evident at all three doses of 10 $\mu\text{g}/\text{kg}$, 30 $\mu\text{g}/\text{kg}$ and 45 $\mu\text{g}/\text{kg}$; (B) A trend in reduction of bilirubin was evident at all three doses of 10 $\mu\text{g}/\text{kg}$, 30 $\mu\text{g}/\text{kg}$ and 45 $\mu\text{g}/\text{kg}$; (C) Leukocytes count remained unchanged across the cohort at follow up days 28 and 42. (D) MELD score reduction at day 0, 28 and 42. (E) Total bilirubin decreased at day 28 and 42 compared to day 0. (F) Total bilirubin decreased at day 7 compared to day 0.



Supplementary Table 1. Summary of pharmacologic characteristics of F-652.

PK	Dose	Parameter	Mean (±SD)	Mean (Min-Max)	
Day 1	10 µg/kg	AUC _{0-t} (h*ng/mL)	6290 (±1430)		
		C _{max} (ng/mL)	125 (±33.2)		
		C _{last} (ng/mL)	53.4 (±15.8)		
		T _{max} (h)		72.0 (68.6-75.5)	
		T _{last} (h)		6.22 (5.25-8.00)	
	30 µg/kg	AUC _{0-t} (h*ng/mL)	23200 (±11400)		
		C _{max} (ng/mL)	450 (±159)		
		C _{last} (ng/mL)	257 (±119)		
		T _{max} (h)		72.2 (65.1-76.4)	
		T _{last} (h)		7.75 (4.72-75.4)	
	45 µg/kg	AUC _{0-t} (h*ng/mL)	43900 (±9020)		
		C _{max} (ng/mL)	1160 (±1100)		
		C _{last} (ng/mL)	442 (±175)		
T _{max} (h)			72.1 (70.1-75.0)		
T _{last} (h)			7.50 (1.00-7.75)		
Day 7	10 µg/kg	AUC _{0-t} (h*ng/mL)	7510 (±6540)		
		AUC _{0-inf} (h*ng/mL)	4890 (±1870)		
		AUC ₀₋₇₂ (h*ng/mL)	2300 (±304)		
		C _{last} (ng/mL)	14.0 (±9.26)		
		C _{max} (ng/mL)	75.1 (±17.4)		
		Residual area (%)	22.2 (±3.49)		
		K _{el} (1/h)	0.0100 (±0.00828)		
		T _½ (h)	105 (±86.3)		
		V _z (L)	18.7 (±4.41)		
		Cl (L/h)	0.169 (±0.110)		
		T _{last} (h)		316 (93.3-647)	
		T _{max} (h)		6.18 (5.43-7.58)	
		30 µg/kg	AUC _{0-t} (h*ng/mL)	65400 (±36700)	
			AUC _{0-inf} (h*ng/mL)	69700 (±37000)	
	AUC ₀₋₇₂ (h*ng/mL)		16600 (±4490)		
	C _{last} (ng/mL)		17.4 (±7.68)		
	C _{max} (ng/mL)		405 (±148)		
	Residual area (%)		7.10 (±2.73)		
	K _{el} (1/h)		0.00430 (±0.00255)		
	T _½ (h)		196 (±87.6)		
	V _z (L)		10.2 (±3.37)		
	Cl (L/h)		0.0386 (±0.00910)		
	T _{last} (h)			982 (310-986)	
	T _{max} (h)			8.27 (4.88-22.4)	
	45 µg/kg		AUC _{0-t} (h*ng/mL)	122000 (±69400)	
			AUC _{0-inf} (h*ng/mL)	108000 (±90800)	
		AUC ₀₋₇₂ (h*ng/mL)	33700 (±11200)		
		C _{last} (ng/mL)	179 (±283)		
C _{max} (ng/mL)		715 (±191)			
Residual area (%)		4.10 (±0.151)			
K _{el} (1/h)		0.00354 (±0.000144)			
T _½ (h)		196 (±7.97)			
V _z (L)		16.1 (±13.7)			
Cl (L/h)		0.0559 (±0.0463)			
T _{last} (h)			818 (314-822)		
T _{max} (h)			7.75 (1.03-8.33)		

Supplementary Table 2. Dose proportionality evaluation for F-652.

Dose Proportionality				
Day 1	AUC_{0-t}	AUC_{0-t} (normalized)	C_{max}	C_{max} (normalized)
10 µg/kg to 30 µg/kg (3-fold increase)	3.7	1.01	3.6	1.02
10 µg/kg to 45 µg/kg (4,5-fold increase)	6.97	1.2	9.28	1.67
Day 7				
10 µg/kg to 30 µg/kg (3-fold increase)	8.7	2.77	5.4	1.78
10 µg/kg to 45 µg/kg (4,5-fold increase)	16.2	3.46	9.5	1.92

Supplementary Table 3. Accumulation ratios for F-652.

Parameter	Dose	Ratio
AUC _{0-t}	10 µg/kg	1.19
	30 µg/kg	2.81
	45 µg/kg	2.77
AUC ₀₋₇₂	10 µg/kg	0.42
	30 µg/kg	0.77
	45 µg/kg	0.79
C _{max}	10 µg/kg	0.6
	30 µg/kg	0.9
	45 µg/kg	0.62

Supplementary Table 4. Propensity score matching analysis for F-652 treatment cohort vs. historical retrospective and prospective cohorts ensuring accurate and non-biased comparison of data between the treatment and control groups. Means are more comparable in the matched cohort and eQQ (quartile differences) values are smaller, both indicating better matching of comparison groups when compared to unmatched cohorts.

	Means (F-652)	Means (historical cohort)	SD (historical cohort)	Mean difference	eQQ median	eQQ mean	eQQ maximum	p-value (vs. F- 652 cohort)
F-652 vs. retrospective cohort (unmatched data)								
Distance	0.4498	0.2078	0.1685	0.2420	0.2409	0.2359	0.3979	-
MELD	20.3529	26.6222	6.9553	-6.2693	5.0000	6.4118	20	0.001
Age	48.9412	48.1333	11.4765	0.8078	2.0000	3.1176	10	0.8
Sex (males)	0.7059	0.6889	0.4682	0.0170	0.0000	0.0588	1.0000	0.9
F-652 vs. retrospective cohort (matched data)								
Distance	0.4498	0.3507	0.1536	0.0992	0.073	0.0999	0.3242	-
MELD	20.3529	21.8824	2.5466	-1.5294	1.000	2.0000	5.0000	0.21
Age	48.9412	50.1765	9.9451	-1.2353	4.000	2.7647	4.0000	0.72
Sex (males)	0.7059	0.7647	0.4372	-0.0588	0.000	0.0588	1.0000	0.7
F-652 vs. prospective cohort (unmatched data)								
Distance	0.4631	0.3380	0.1867	0.1251	0.1381	0.1393	0.2254	-
MELD	20.3529	24.5926	7.3968	-4.2397	4.0000	4.5882	15.0000	0.04
Age	48.9412	49.0000	14.0165	-0.0588	4.0000	4.7059	11.0000	0.99
Sex (males)	0.7059	0.5926	0.5007	0.1133	0.0000	0.1176	1.0000	0.44
F-652 vs. prospective cohort (matched data)								
Distance	0.4631	0.4395	0.1530	0.0236	0.0336	0.0320	0.0679	-
MELD	20.3529	21.4118	5.7777	-1.0588	2.0000	2.0000	4.0000	0.55
Age	48.9412	47.0000	13.6657	1.9412	4.0000	4.6471	9.0000	0.64
Sex (males)	0.7059	0.7059	0.4697	0.0000	0.0000	0.0000	0.0000	1.0
F-652 vs. steroid treated AH cohort (unmatched data)								

Distance	0.6059	0.3350	0.1975	0.2709	0.3254	0.2855	0.4161	-
MELD	20.3529	24.400	2.7796	-4.0471	4.0000	3.8235	6.0000	0.002
Age	48.9412	45.700	11.7791	3.2412	5.0000	4.4706	10.0000	0.39
Sex (males)	0.7059	0.600	0.5026	0.1059	0.0000	0.1176	1.0000	0.52
F-652 vs. steroid treated AH cohort (matched data)								
Distance	0.6059	0.3721	0.1911	0.2338	0.2743	0.2353	0.3268	-
MELD	20.3529	23.8824	2.6899	-3.5294	4.0000	3.5294	6.0000	0.006
Age	48.9412	46.5882	12.5900	2.3529	3.0000	3.6471	10.0000	0.55
Sex (males)	0.7059	0.7059	0.4697	0.0000	0.0000	0.0000	0.0000	1.0

Supplementary Table 5. Baseline clinical characteristics of propensity score matched controls from three historical cohorts compared against the F-652 treated cohort.

	Retrospective AH Cohort	Prospective AH Cohort	Steroid treated AH Cohort
Age	50.94 ± 9.44	47 ± 13.26	46.59 ± 12.21
Sex (fraction male)	0.75	0.71	0.71
MELD	21.63 ± 2.32	21.41 ± 5.61	23.88 ± 2.61
Creatinine (mg/dL)	0.66 ± 0.24	0.75 ± 0.22	0.82 ± 0.36
INR	1.6 ± 0.18	n/a	1.88 ± 0.47
Bilirubin (mg/dL)	17.57 ± 8.61	15.2 ± 9.18	16.01 ± 7.02
PT (sec)	16.81 ± 2.37	18.43 ± 7.02	20.92 ± 4.36

Supplementary Table 6. Multiplex analysis for serum levels of proinflammatory and regenerative biomarkers (fold change over baseline) at day 28 and 42.

Biomarkers	Day 0	Day 28	p-value	Day 42	p-value
Angioproten2	1 ± 0.06	1.02 ± 0.11	0.9924	1.15 ± 0.11	0.6609
CCL17	1 ± 0.18	0.90 ± 0.09	0.8284	0.83 ± 0.09	0.5907
CCL20	1 ± 0.08	0.66 ± 0.14	0.1471	0.62 ± 0.11	0.0955
CCL3	1 ± 0.07	0.96 ± 0.09	0.9698	1.13 ± 0.11	0.7307
CCL4	1 ± 0.07	1.11 ± 0.06	0.7971	1.19 ± 0.09	0.5217
CCL5	1 ± 0.08	0.77 ± 0.05	0.3938	0.74 ± 0.06	0.3102
CRP	1 ± 0.07	0.64 ± 0.08	0.1191	0.41 ± 0.06	0.0053
CXCL1	1 ± 0.08	1.16 ± 0.16	0.6257	1.04 ± 0.08	0.9698
CXCL10	1 ± 0.59	0.90 ± 0.09	0.8284	0.85 ± 0.05	0.6609
CXCL11	1 ± 0.15	0.69 ± 0.06	0.1982	0.56 ± 0.04	0.0465
CXCL5	1 ± 0.06	2.19 ± 0.28	<0.0001	2.01 ± 0.17	<0.0001
CXCL9	1 ± 0.09	1.08 ± 0.10	0.8858	1.15 ± 0.06	0.6609
Eotaxin	1 ± 0.12	1.13 ± 0.07	0.7307	1.09 ± 0.08	0.8581
FGF-β	1 ± 0.08	1.24 ± 0.10	0.3647	1.33 ± 0.08	0.1629
G-CSF	1 ± 0.12	0.96 ± 0.08	0.9698	1.21 ± 0.12	0.4557
HGF	1 ± 0.07	0.51 ± 0.04	0.0239	0.60 ± 0.06	0.0759
IL-10	1 ± 0.07	0.67 ± 0.03	0.1629	0.59 ± 0.03	0.0674
IL-1α	1 ± 0.18	1.57 ± 0.26	0.0073	3.02 ± 0.36	<0.0001
IL-27	1 ± 0.08	1.24 ± 0.10	0.3647	1.33 ± 0.08	0.1629
IL-6	1 ± 0.06	0.61 ± 0.06	0.0852	0.80 ± 0.11	0.4883
IL-8	1 ± 0.07	0.45 ± 0.07	0.0099	0.79 ± 0.16	0.4557
MCP-1	1 ± 0.08	0.75 ± 0.04	0.3367	0.77 ± 0.05	0.3938
MPO	1 ± 0.18	1.83 ± 0.36	<0.0001	1.49 ± 0.18	0.0239
NGAL	1 ± 0.30	0.75 ± 0.14	0.3367	1.17 ± 0.18	0.5907
PDGF-AA	1 ± 0.07	1.20 ± 0.08	0.4883	1.27 ± 0.12	0.2850
PDGF-BB	1 ± 0.06	1.09 ± 0.07	0.8581	1.15 ± 0.10	0.6609
SCF	1 ± 0.10	1.46 ± 0.16	0.0359	2.05 ± 0.15	<0.0001
sFas	1 ± 0.06	1.05 ± 0.09	0.9534	1.06 ± 0.09	0.9337
sFasL	1 ± 0.17	0.34 ± 0.02	0.0016	0.57 ± 0.03	0.0528
TNFα	1 ± 0.19	1.16 ± 0.15	0.6257	1.05 ± 0.13	0.9534

CCL17: Chemokine (C-C motif) ligand 17 [also known as TARC]; CCL20: Chemokine (C-C motif) ligand 20 [also known as MIP-3 α]; CCL3: Chemokine (C-C motif) ligand 3 [also known as MIP-1 α]; CCL4: Chemokine (C-C motif) ligand 4 [also known as MIP-1 β]; CCL5: Chemokine (C-C motif) ligand 5 [also known as RANTES]; CRP: C-reactive protein; CXCL1: C-X-C motif chemokine 1 (also known as GRO α); CXCL10: C-X-C motif chemokine 10 (also known as IP-10); CXCL11: C-X-C motif chemokine 11 (also known as I-TAC); CXCL5: C-X-C motif chemokine 5 (also known as ENA-78); CXCL9: C-X-C motif chemokine 9 (also known as MIG); FGF- β : fibroblast growth factor β ; G-CSF: Granulocyte colony-stimulating factor; HGF: Hepatocyte growth factor; IL-10: Interleukin-10; IL-1 α : Interleukin-1 α ; IL-27: Interleukin-27; IL-6: Interleukin-6; IL-8: Interleukin-8; MCP-1: Monocyte Chemoattractant Protein-1; MPO: Myeloperoxidase; NGAL: Neutrophil gelatinase-associated lipocalin; PDGF: Platelet-derived growth factor; SCF: Stem cell factor; TNF α : Tumor necrosis factor α .

Supplementary Table 7. Multiplex analyses for serum levels of proinflammatory and regenerative biomarkers at day 42 divided by dose.

	Percentage of baseline value at day 42			
	10 µg/kg dose	30 µg/kg dose	45 µg/kg dose	All doses
Angioproten2	50.4	76.8	249.2	114.9
CCL17	48.9	257.1	137.7	83.1
CCL20	13.1	50.2	177.2	62.2
CCL3	79.6	199	90.5	113.2
CCL4	78.7	118.4	123.4	119.1
CCL5	30.4	170.8	119.8	74
CRP	11.4	68.1	44	41.4
CXCL1	55.8	164.7	90.2	104.4
CXCL10	53	102.9	102.7	84.8
CXCL11	24.8	202.2	31.4	55.6
CXCL5	112.7	197.1	287.1	201.2
CXCL9	96.2	125	192.5	115.3
Eotaxin	67.2	66.1	249.8	108.9
FGF-b	106.6	118.1	147.2	133.4
G-CSF	86.3	203.3	72.4	121.3
HGF	19.7	41	130.2	59.9
IL-10	65.8	86.4	42.9	59.3
IL-1a	137.5	828.3	195.5	302.4
IL-1b	245.2	625.9	63.6	150.2
IL-27	106.6	118.1	147.2	133.4
IL-6	26.8	107.9	85.9	79.8
IL-8	25.4	25.3	215.8	79.1
MCP-1	36.7	78.7	110.1	77.4
MPO	5.9	238.2	403.8	149.3
NGAL	2.6	503.3	1032.2	116.9
PDGF-AA	41.1	277	113.7	127.3
PDGF-BB	48.2	165.4	103.7	114.6
SCF	198	124.8	294.1	205.4
sFas	55.5	91.4	174.4	106.1
sFasL	428.7	98	47.6	57.3
TNFa	214.9	1165.7	32.7	105.4

CCL17: Chemokine (C-C motif) ligand 17 [also known as TARC]; CCL20: Chemokine (C-C motif) ligand 20 [also known as MIP-3 α]; CCL3: Chemokine (C-C motif) ligand 3 [also known as MIP-1 α]; CCL4: Chemokine (C-C motif) ligand 4 [also known as MIP-1 β]; CCL5: Chemokine (C-C motif) ligand 5 [also known as RANTES]; CRP: C-reactive protein; CXCL1: C-X-C motif chemokine 1 (also known as GRO α); CXCL10: C-X-C motif chemokine 10 (also known as IP-10); CXCL11: C-X-C motif chemokine 11 (also known as I-TAC); CXCL5: C-X-C motif chemokine 5 (also known as ENA-78); CXCL9: C-X-C motif chemokine 9 (also known as MIG); FGF- β : fibroblast growth factor β ; G-CSF: Granulocyte colony-stimulating factor; HGF: Hepatocyte growth factor; IL-10: Interleukin-10; IL-1 α : Interleukin-1 α ; IL-27: Interleukin-27; IL-6: Interleukin-6; IL-8: Interleukin-8; MCP-1: Monocyte Chemoattractant Protein-1; MPO: Myeloperoxidase; NGAL: Neutrophil gelatinase-associated lipocalin; PDGF: Platelet-derived growth factor; SCF: Stem cell factor; TNF α : Tumor necrosis factor α .