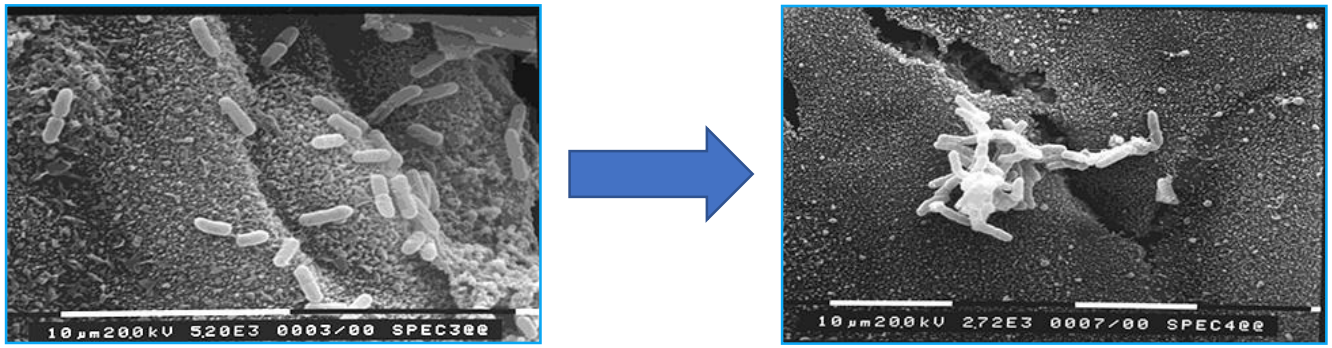
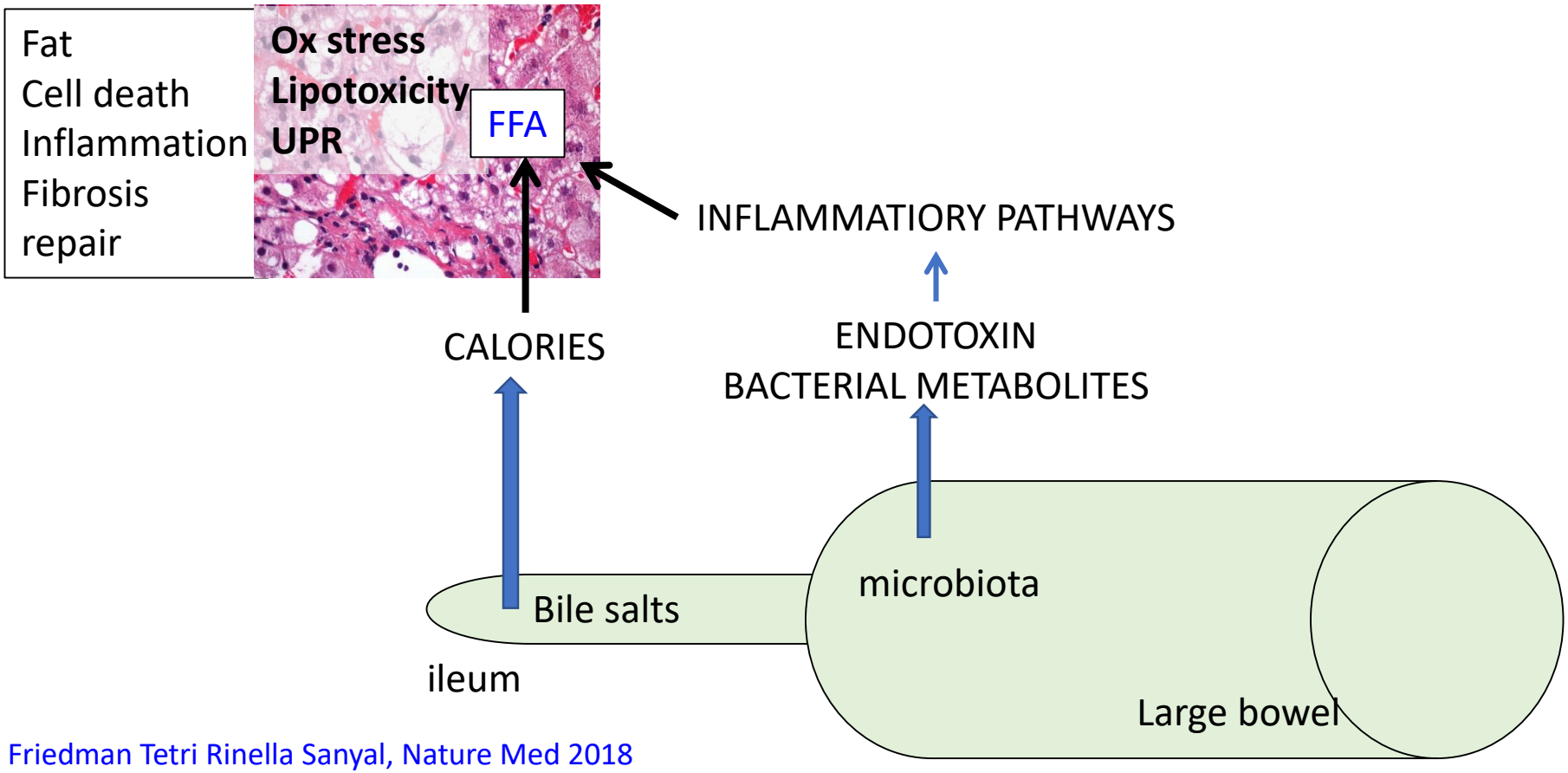
IMM-124E IMPROVES METABOLIC ENDOTOXEMIA AND MARKERS OF LIVER INJURY IN NONALCOHOLIC STEATOHEPATITIS



Abdelmalek MF, Freilich BL, Harrison S, Powell EE, Rinella ME, Tobis N, Peres D, Kanellos J, Lalazar G, Sanyal AJ

Study Sponsor: Immuron (NCT02316717)

Metabolic endotoxemia: a driver of systemic inflammation in obesity-insulin resistance-type 2 diabetes



Friedman Tetri Rinella Sanyal, Nature Med 2018
Stavros B et al. Molecular Metabolism, 2016
Sharifnia T, et al. Am J Physiol Gastrointest Liver Physiol 2015

IMM-124E

Pre-Clinical Studies

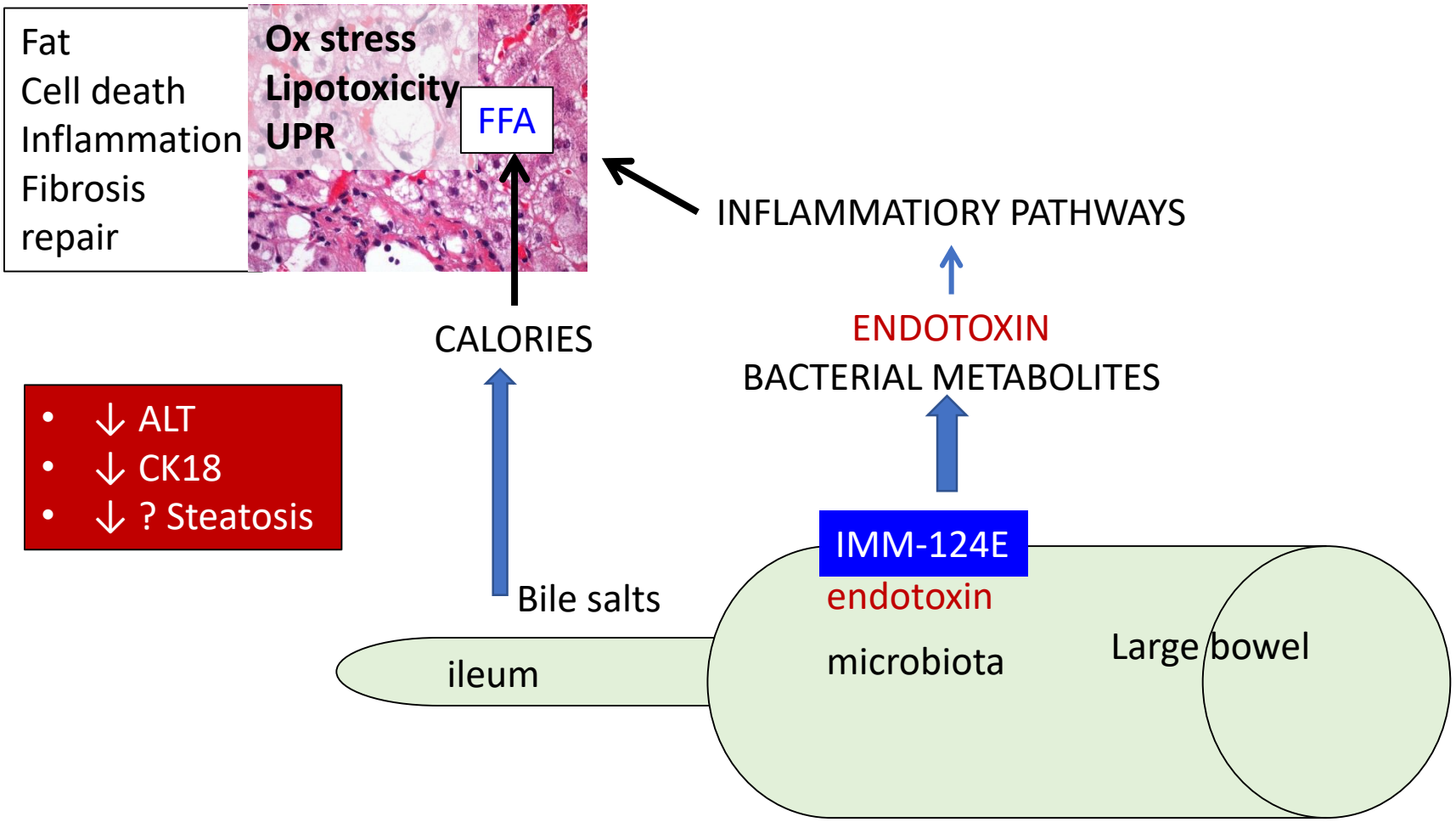
- Colostrum from cattle vaccinated with pathogenic Enterotoxigenic E. coli (ETEC) (>35% IgG)
- Orally active antibodies bind and neutralize endotoxins
- Reduces motility, adherence to host epithelium and colonization of pathogenic ETEC

Without IMM-124E
Bacteria attach to gut wall and infect

With IMM-124E Decreased Bacterial adherence and colonization

Sears et al. Clinical & Vaccine Immunology 2017;24(8)
Scanning Electron Micrographs courtesy of Immuron Limited

Hypothesis: Decreasing metabolic endotoxemia with IMM-124E will reduce the drivers of NASH progression

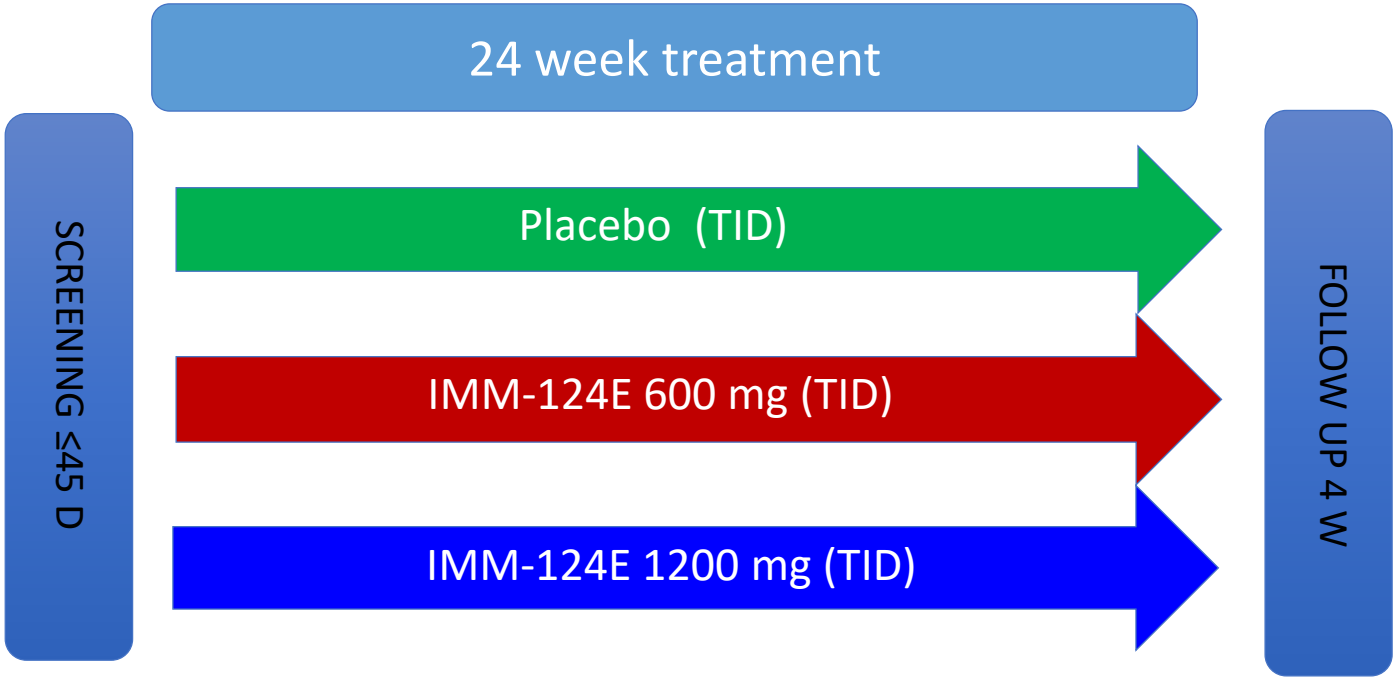


STUDY DESIGN:
Prospective dose-ranging phase 2A trial

120 patients, 3-arms, Randomized, double blind, Placebo controlled

2-dose, balanced 1:1:1 design

Treatment allocation stratified by diabetes status:
HBA1C <6.0 versus HBA1C >6.0 and/or diagnosis of Type II diabetes



Key Inclusion Criteria

- Age ≥ 18 years
- Diagnosis of NASH

  Histologically proven within 12 months of screening

  and all of the following criteria met:

  - NASH activity score (NAS) of 4 or more
  - Cytologic ballooning score of at least 1
  - 10% or more macrovesicular steatosis
  - Hematoxylin & Eosin (H&E) stained slides and/or paraffin block available for independent assessment

- HBA1C of ≤9.0

Key Exclusion Criteria

- Liver disease of other cause
- Cirrhosis
- BMI ≤25kg/m^2
- Alcohol use ≥30g/day
- Weight change of ≥ 10% in past 12 months

- Other excluded conditions:

  T1DM, ongoing multi-systemic immune-mediated disease, concurrent or past malignant disease

- Concurrent medications including:

  Immune modulatory agents, antibiotics, or probiotics

  Change in dose of Vitamin E, Glitazones, Gliptins and GLP1 analogs, Insulin, gemfibrozil or statins prior to determinant biopsy

- Cow milk allergy, lactose intolerance

Study Endpoints

PRIMARY

- Safety and tolerability (clinical)
- Hepatic Fat Fraction

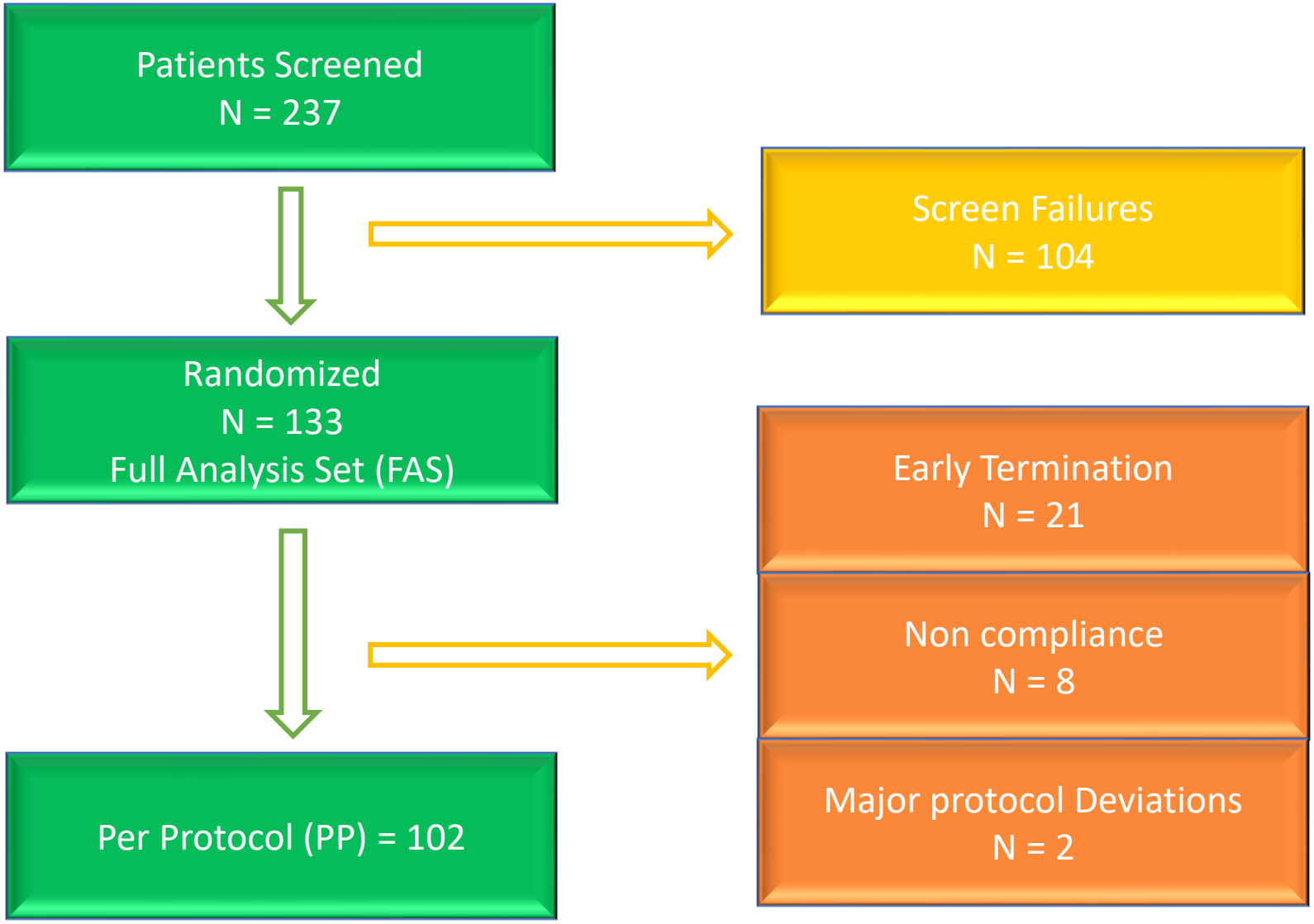
SECONDARY

- Markers of liver injury – ALT, AST, CK-18
- Glucose homeostasis
- Serum Bovine Ig – Safety parameter
- Establish recommended dose

MoA

- Lipopolysaccharides (LPS)

Results: Study Population



Results: baseline characteristics

	Placebo (n=44)	IMM-124E 600 mg (n=43)	IMM-124E 1200 mg (n=46)	P value
Age (yrs)	49.4	52.5	50.9	0.579
Females (%)	45.5	53.5	58.7	0.410
Caucasian (%)	76.3	72.4	88.6	0.236
T2 DM (%)	38.6	41.9	39.1	0.987
BMI (kg/m^2)	34.7	33.8	34.2	0.786
AST (IU/l)	47.8	48.0	46.7	0.968
ALT (IU/l)	70.9	79.9	67.3	0.422
Alk Phos (IU/l)	83.7	88.5	79.9	0.536
Bilirubin (mg/dl)	0.62	0.63	0.68	0.798
HbA1C (%)	7.8	7.3	6.1	0.382
MRI-PDFF (%)	18.1	20.2	19.6	0.559

*Group mean values

Results: baseline histology

	Placebo (n=44)	IMM-124E 600 mg (n=43)	IMM-124E 1200 mg (n=46)	P value
steatosis	2.24	2.24	2.14	0.825
Lobular inflammation	1.71	1.59	1.66	0.647
Ballooning	1.39	1.45	1.5	0.598
Fibrosis	1.66	1.72	1.69	0.952
NAS	5.34	5.28	5.31	0.968

Individual parameters scored by NASH CRN scoring system- *Kleiner et al 2005*

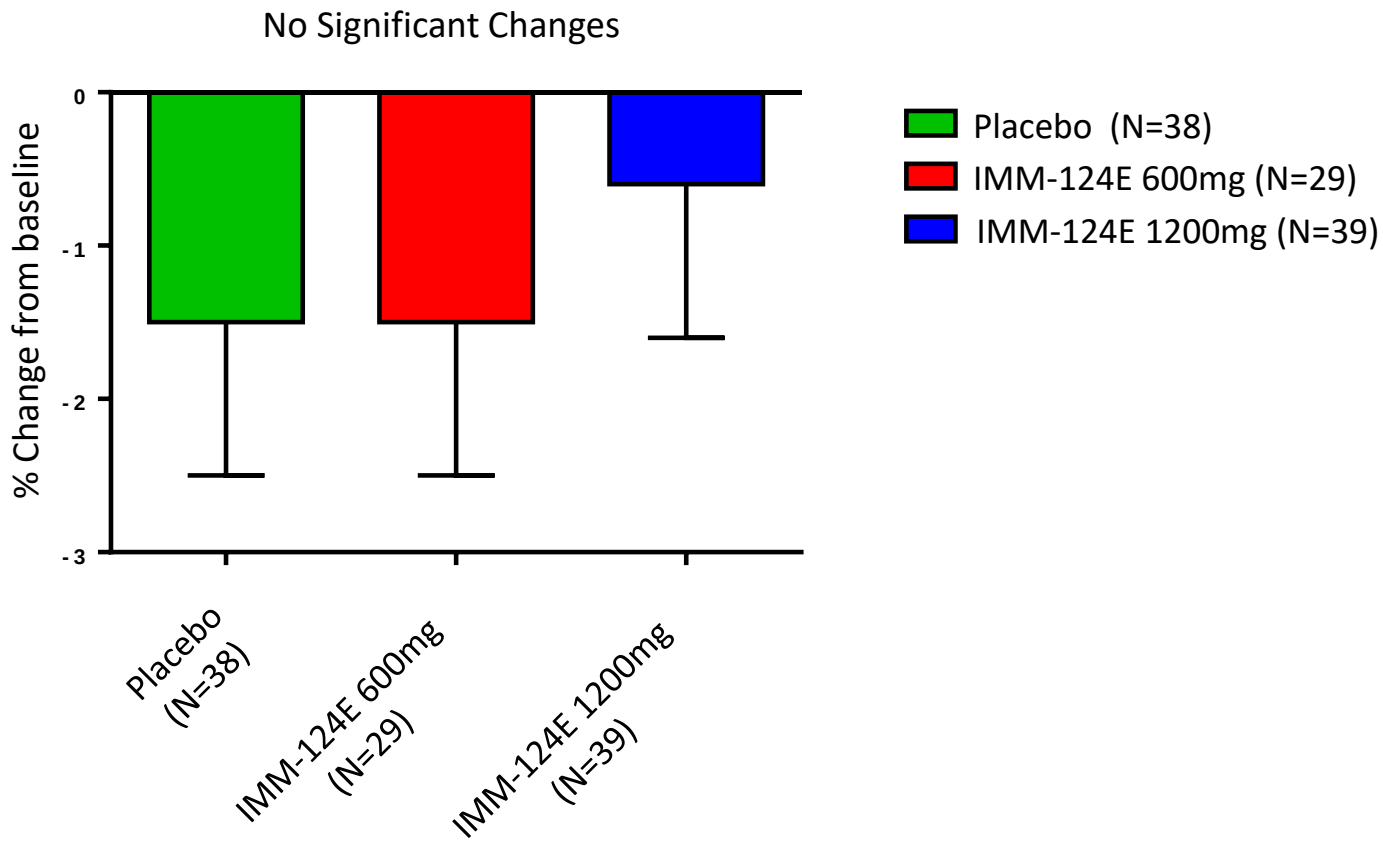
Primary outcome: Serious Adverse Events

	Placebo (n=44)	IMM-124E 600 mg (n=43)	IMM-124E 1200 mg (n=46)
Any	3	1	2
Chest pain	0	0	1
Motor vehicle accident	1	0	0
Elevated CPK	1	0	0
Transitional cell CA	0	1	0
Anxiety attacks	0	0	1
Psychiatric hospitalization	1	0	0
Rx stopped due to AE	0	1	1
Grade 3-4	1	1	2
Grade 5 (Death)	1	0	0

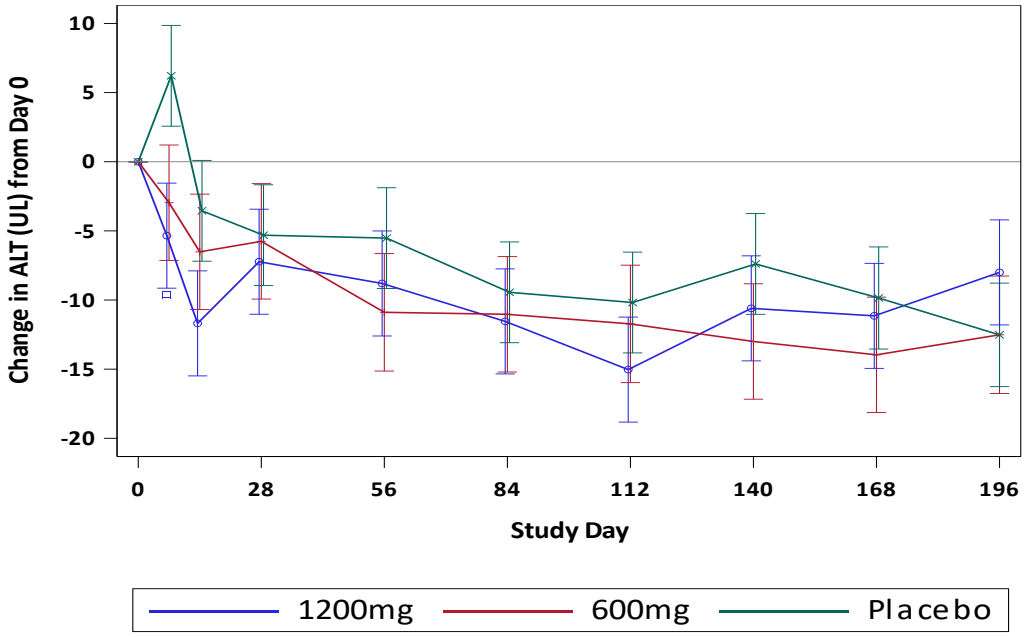
* p = NS
* Serious adverse events defined per CTCAE (5.0) criteria

Primary outcome: MRI-PDFF

No significant changes

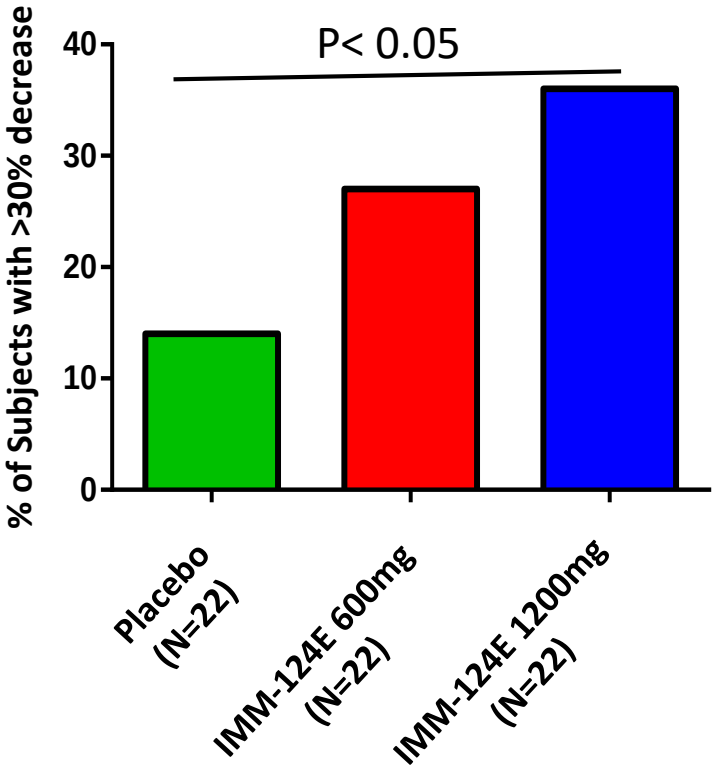


Secondary outcome: ALT



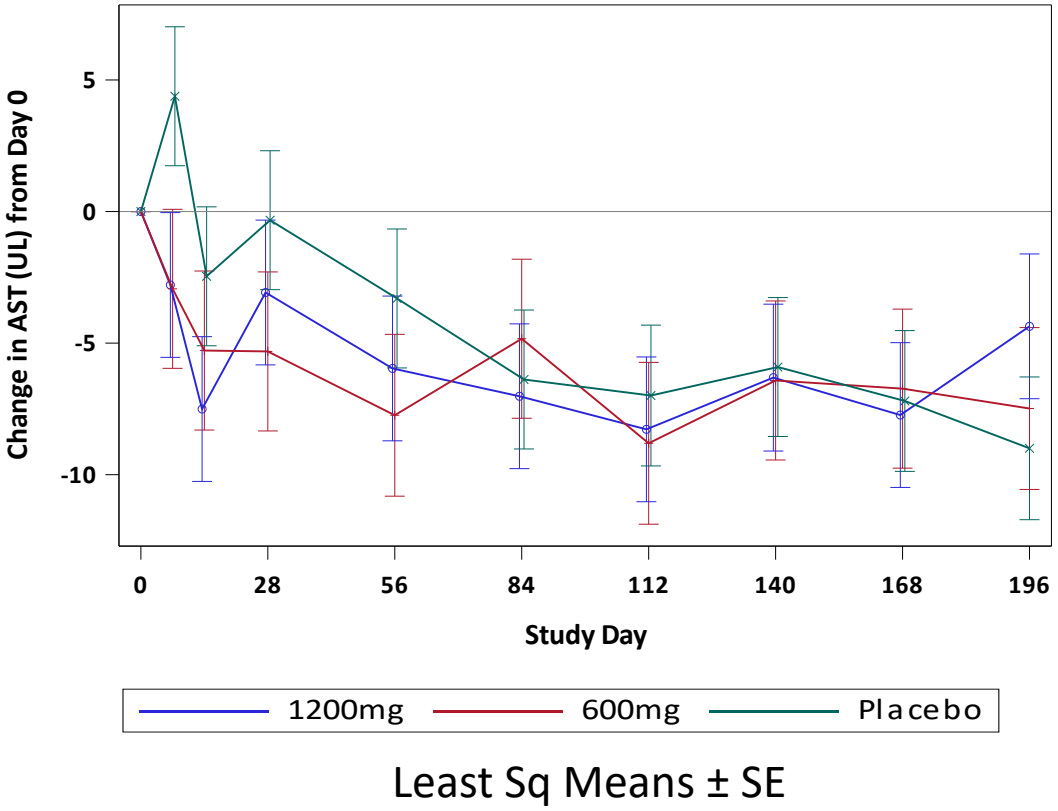
Least Sq Means ± SE

Proportion with ≥30% decrease in ALT (Baseline ALT ≥50)

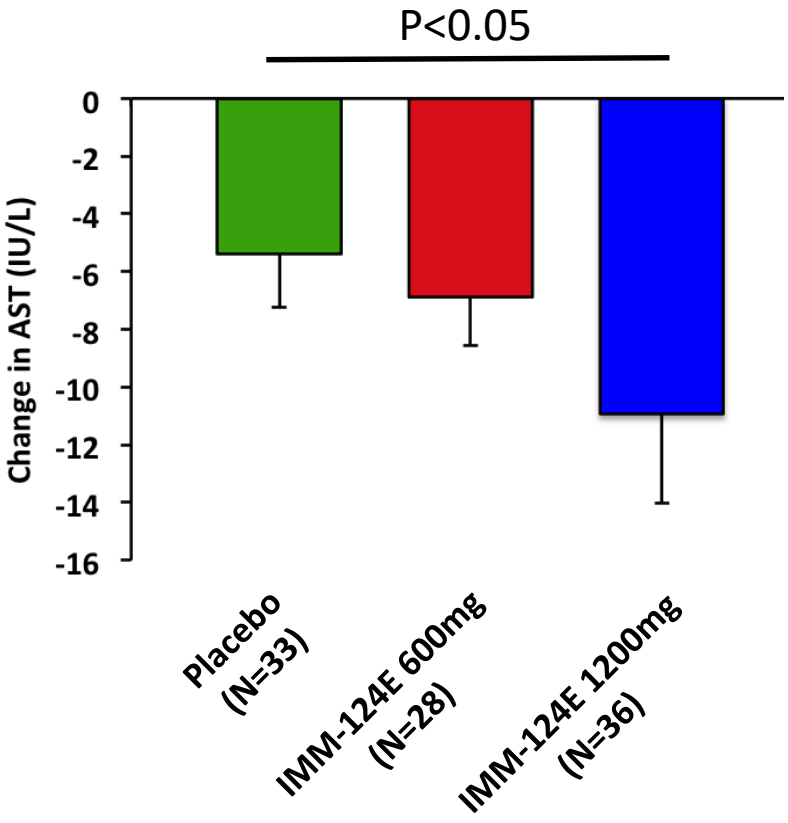


* Sites < 3 subjects excluded

Markers of liver injury: IMM-124E improved AST

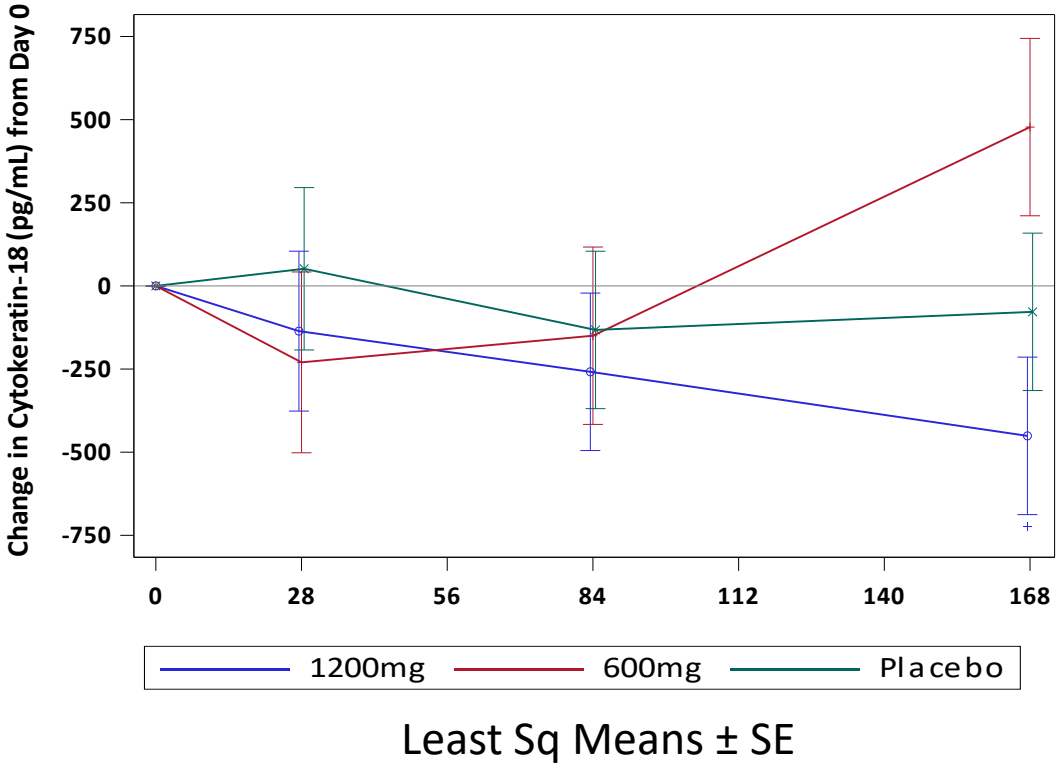


Least Sq Means ± SE

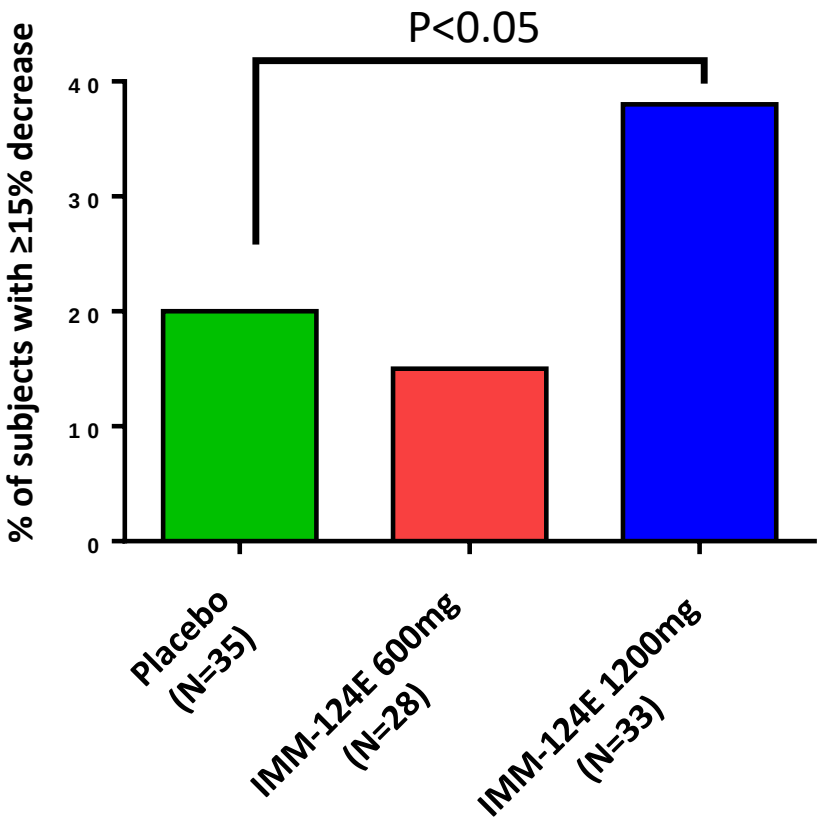


*Sites < 3 subjects excluded

Baseline to End of Treatment changes in CK 18



Proportion with ≥15% decrease in CK-18

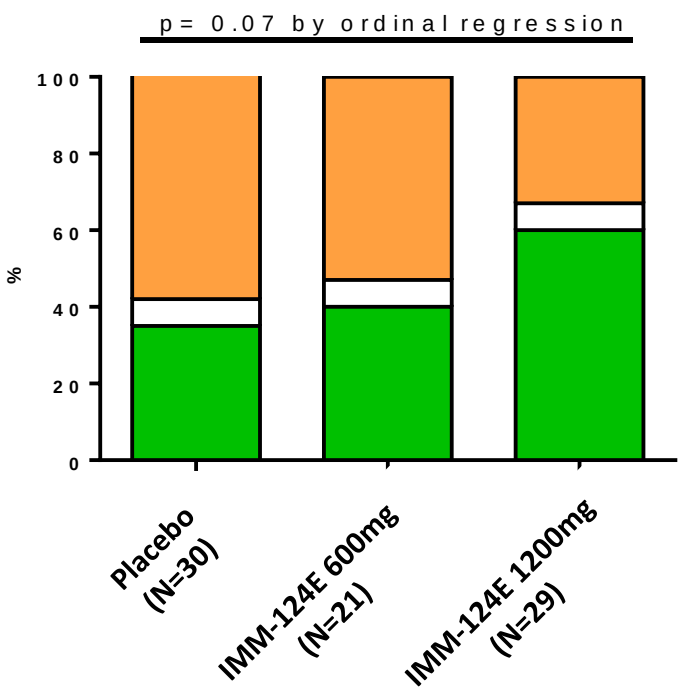


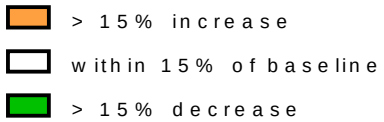
* Sites < 3 subjects excluded

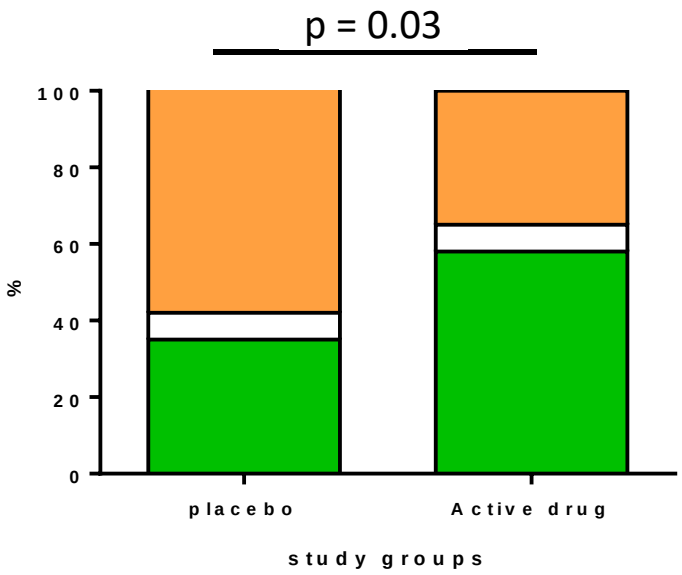
IMM-124E does not impact insulin resistance (HOMA-IR)

	placebo	IMM-124E 600 mg	IMM-124E 1200 mg
Mean Baseline	11.78	9.68	9.51
SD Baseline	9.84	6.76	8.04
Mean W24	10.84	11.37	9.89
SD W24	8.68	12.26	7.13
P value vs. Placebo		0.236	0.491

Mechanism of action related endpoints: IMM-124E (1200 mg) decreased endotoxemia







* PP population
* Sites < 3 subjects excluded
* LPS < 250 (ng/ml) excluded

LPS sensitivity analysis

		IMM-124E 1200mg		placebo		p-value (Wald test)
		# of events	%	# of events	%	
improvement	<-30%	12	42.9%	8	27.6%	0.222
	<-25%	14	50.0%	8	27.6%	0.075
	<-20%	15	53.6%	10	34.5%	0.139
	<-15%	18	64.3%	10	34.5%	**0.018**
	<-10%	19	67.9%	11	37.9%	**0.018**
	<-5%	19	67.9%	11	37.9%	**0.018**
	<0%	20	71.4%	12	41.4%	**0.016**
deterioration	>30%	6	21.4%	14	48.3%	**0.026**
	>25%	6	21.4%	15	51.7%	**0.012**
	>20%	6	21.4%	15	51.7%	**0.012**
	>15%	7	25.0%	17	58.6%	**0.006**
	>10%	7	25.0%	17	58.6%	**0.006**
	>5%	7	25.0%	17	58.6%	**0.006**
	>0%	8	28.6%	17	58.6%	**0.016**

Summary

- **IMM-124E was well tolerated and had no discernable toxicity**
- **The systemic exposure to bovine IgG was minimal to none**
- **IMM-124E did not improve hepatic steatosis**
- **IMM-124E produced a dose-dependent improvement in endotoxemia and markers of liver injury (AST, ALT, CK 18)**

Conclusions

- **The study provides proof of concept that metabolic endotoxemia can be improved with IMM-124E.**

- **These provide a rationale to evaluate this compound in even higher doses in conditions where endotoxemia may be relevant e.g. alcohol-induced liver injury and cirrhosis.**

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