

The anti-fibrotic agent tipelukast (MN-001) reduces serum triglycerides significantly in NASH and NAFLD patients with hypertriglyceridemia after 8 weeks of treatment, an interim analysis of clinical trial, MN-001-NATG-201

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INTRODUCTION

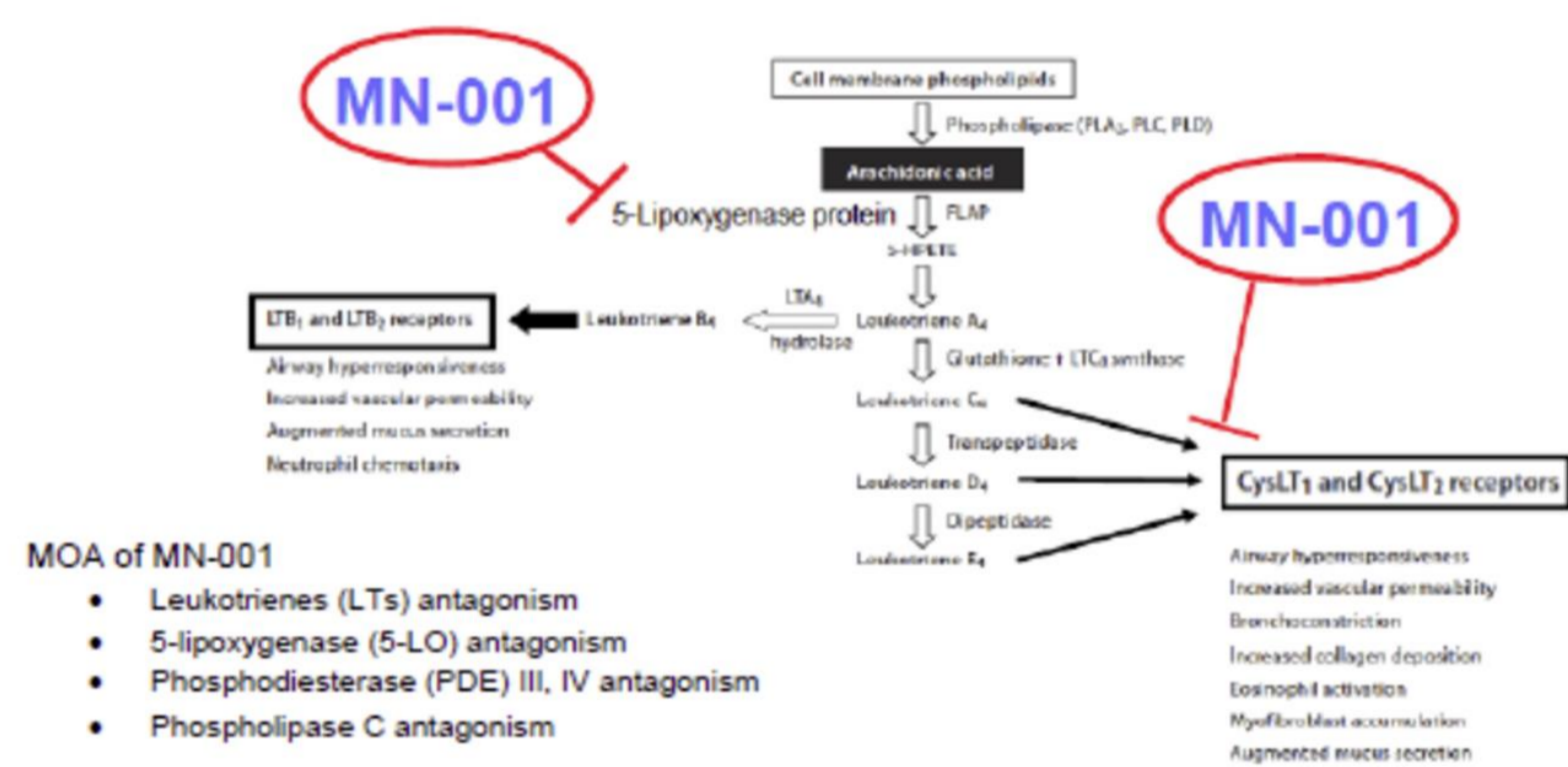
MN-001 (Tipelukast) is a novel, orally available, small molecule. In vitro receptor binding and enzyme inhibition assays have identified several mechanisms including leukotriene (LT) receptor antagonism and inhibition of phosphodiesterases (PDE) 3 and 4, 5-lipoxygenase (5-LO), phospholipase C and thromboxane A2 (Table 1).

Table 1: MN-001's purported anti-inflammatory effects

Assay	Species	IC ₅₀ (K _i) (μM)	MN-001
LT _{C₄} Synthetase	Gp	24.7	
5-LO	Hu	1.11	
PDE1	Bov	0.741	
PDE2	Hu	3.43	
PDE3	Hu	0.567	
PDE4	Hu	0.839	
PDE5	Hu	12.7	
PDE6	Bov	2.05	
PLA2-i	Pig	142	
PLC	Ba	0.89	
Adrenergic α _{2B}	Hu	2.91 (1.28)	
Adrenergic β ₂	Hu	4.63 (3.47)	
Adrenergic NE Transporter	Hu	3.5 (3.47)	
LTB ₄	Hu	9.02 (2.29)	
LTD ₄	Gp	6.36 (3.18)	
Melanocortin MC5	Hu	2.58 (2.42)	
Opiate δ	Hu	1.04 (0.365)	
Thromboxane A2	Hu	3.37 (2.2)	

MN-001 is thought to have potential utility for treating fatty liver disease with its inhibitory effect on 5-LO and the 5-LO/LT pathway, including non-alcoholic steatohepatitis (NASH). (AASLD 2014; Fig. 1).

Figure 1: Mechanism of Action of MN-001



In a NASH mouse model study, MN-001 was shown to significantly decrease NAFLD activity score (NAS) (Fig. 2) and dose-dependently reduce area with fibrosis (Fig. 3).

Figure 2: MN-001 effects on NAFLD activity score in a NASH mouse model

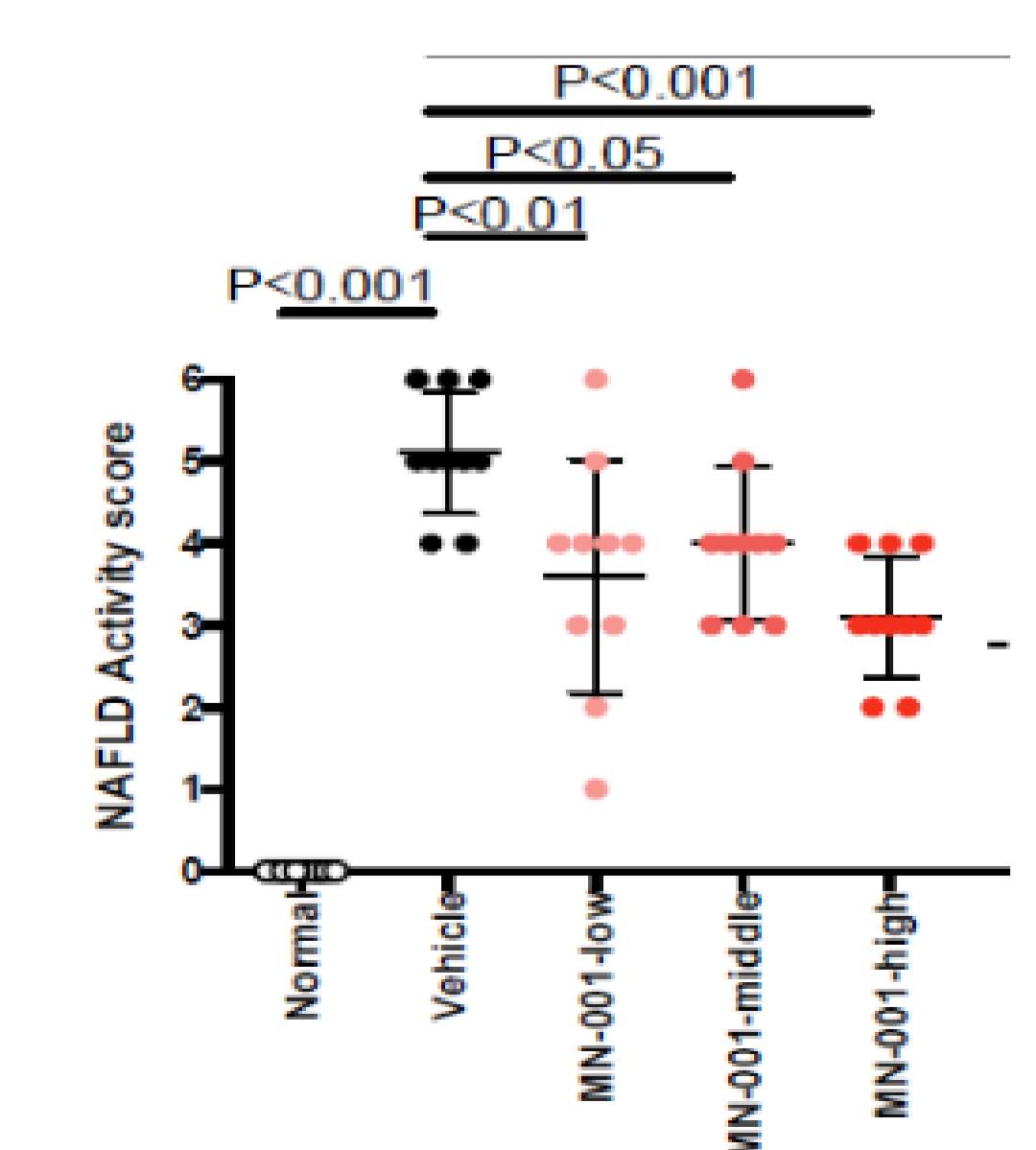
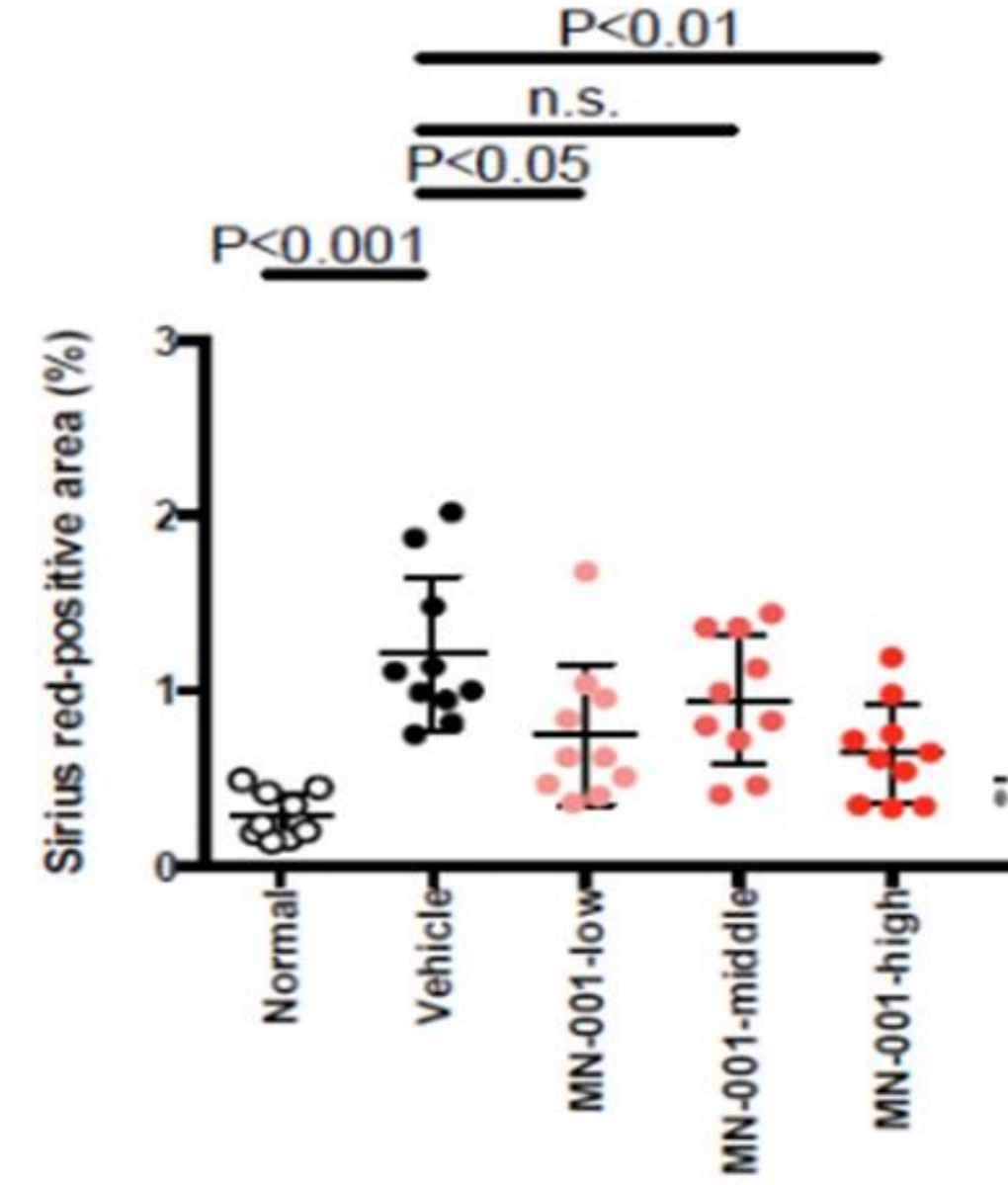


Figure 3: MN-001 effects on area fibrosis in a NASH mouse model



CLINICAL BACKGROUND

The safety of MN-001 has been evaluated in more than 600 subjects in six Phase 1, four Phase 2 trials and one Phase 3 trial to date targeting healthy volunteers and patients with chronic asthma and interstitial cystitis. It was observed that treatment MN-001 reduced serum triglyceride (TG) levels in these clinical studies.

AIM OF STUDY

This is a Phase 2 study to evaluate the effects of MN-001 on serum TG levels in subjects diagnosed with non-alcoholic steatohepatitis (NASH) or non-alcoholic fatty liver disease (NAFLD) with hypertriglyceridemia defined as fasting serum TG level ≥ 150 mg/dL.

METHODOLOGY

This is a multi-center, open-label study designed to evaluate the efficacy, safety, and tolerability of tipelukast (MN-001) in subjects diagnosed with NASH or NAFLD with hypertriglyceridemia (fasting serum TG ≥ 150 mg/dL confirmed at screening).

Subjects receive MN-001 250 mg q.d. for the first 4 weeks and 250 mg b.i.d. for an additional 8 weeks.

INTERIM ANALYSIS

The interim efficacy and safety results of fifteen subjects who completed 8 weeks treatment (250 mg/day for 4 weeks followed by 500 mg/day for 4 weeks) were analyzed.

Two sets of analysis are presented:

- 1) Efficacy results from ALL 15 subjects who completed treatment with MN-001 for 8 weeks (250 mg q.d. for 4 weeks and 250 mg b.i.d. for 4 weeks),
- 2) Efficacy results without the single outlier (14 subjects) who completed treatment with MN-001 for 8 weeks (250 mg q.d. for 4 weeks and 250 mg b.i.d. for 4 weeks).

The rationale for the 2 sets of analysis is based on one subject's inordinately high baseline TG level (Subject 5019-RM pre-treatment result: 1288 mg/dL TG and post-treatment TG: 300 mg/dL) that caused a large variance value in the group's analysis. Therefore, it was decided that the analyses will be reported with and without this subject's results included.

RESULTS

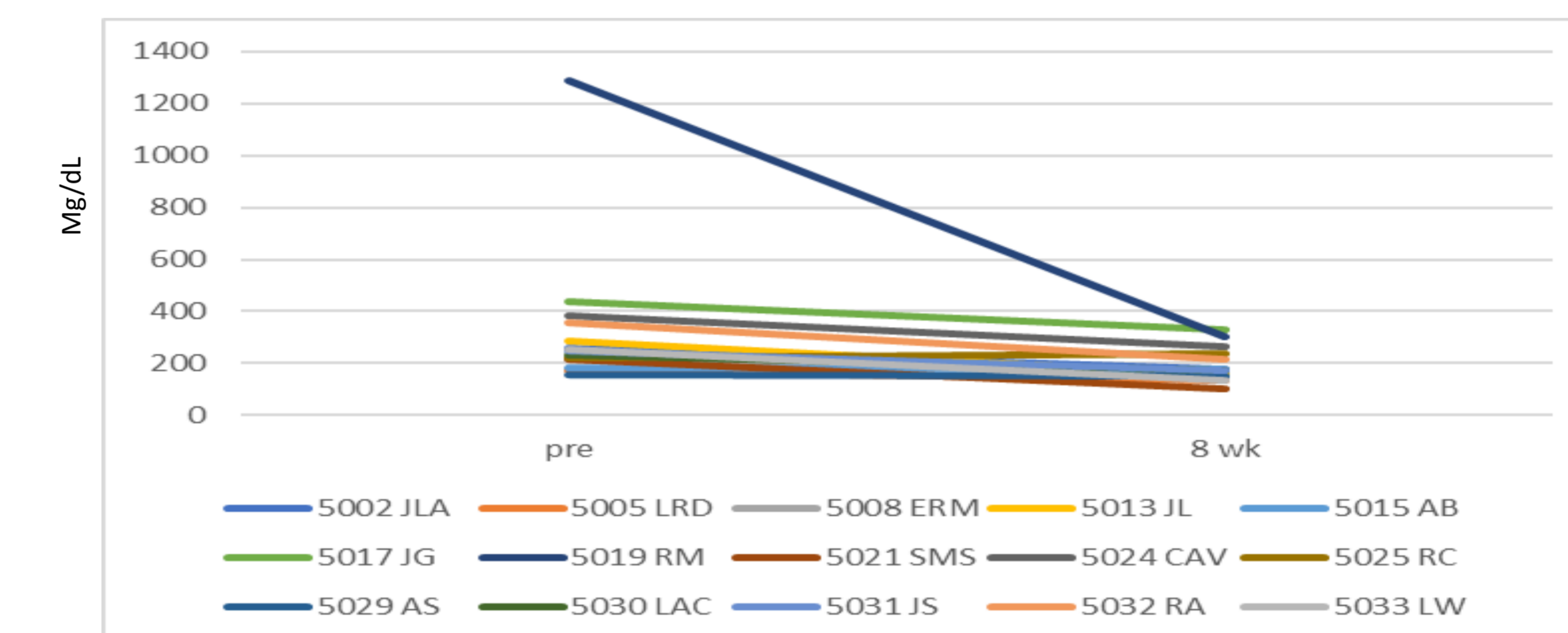
Interim Analysis from ALL 15 Subjects

After 8 weeks of treatment with MN-001 (tipelukast), serum triglyceride levels were reduced in 14 out of 15 subjects (Fig. 4). Pre-treatment mean serum TG was 328.6 mg/dL and post-treatment mean TG was 192.9 mg/dL. MN-001 reduced mean TG by 135.7 mg/dL, resulting in a 41.3% reduction ($p=0.02$) (Table 2). There were no clinically significant safety and tolerability issues.

Table 2: Effects of Tipelukast on Mean Triglyceride Levels after 8 weeks of Treatment (t-test: Paired Two Sample for Means)

t-Test: Paired Two Sample for Means	Pre-treatment	Week 8	Change
Mean serum TG level (mg/dL)	328.6	192.9	- 135.7 (- 41.3 %)
Variance	76753.7	4234	
Sample size	15	15	
Pearson Correlation		0.63	
Hypothesized Mean Difference		0	
df		14	
t Stat		2.2	
P-value		0.02	

Figure 4: Changes in Individual Subject serum TG Levels after 8 week MN-001 Treatment



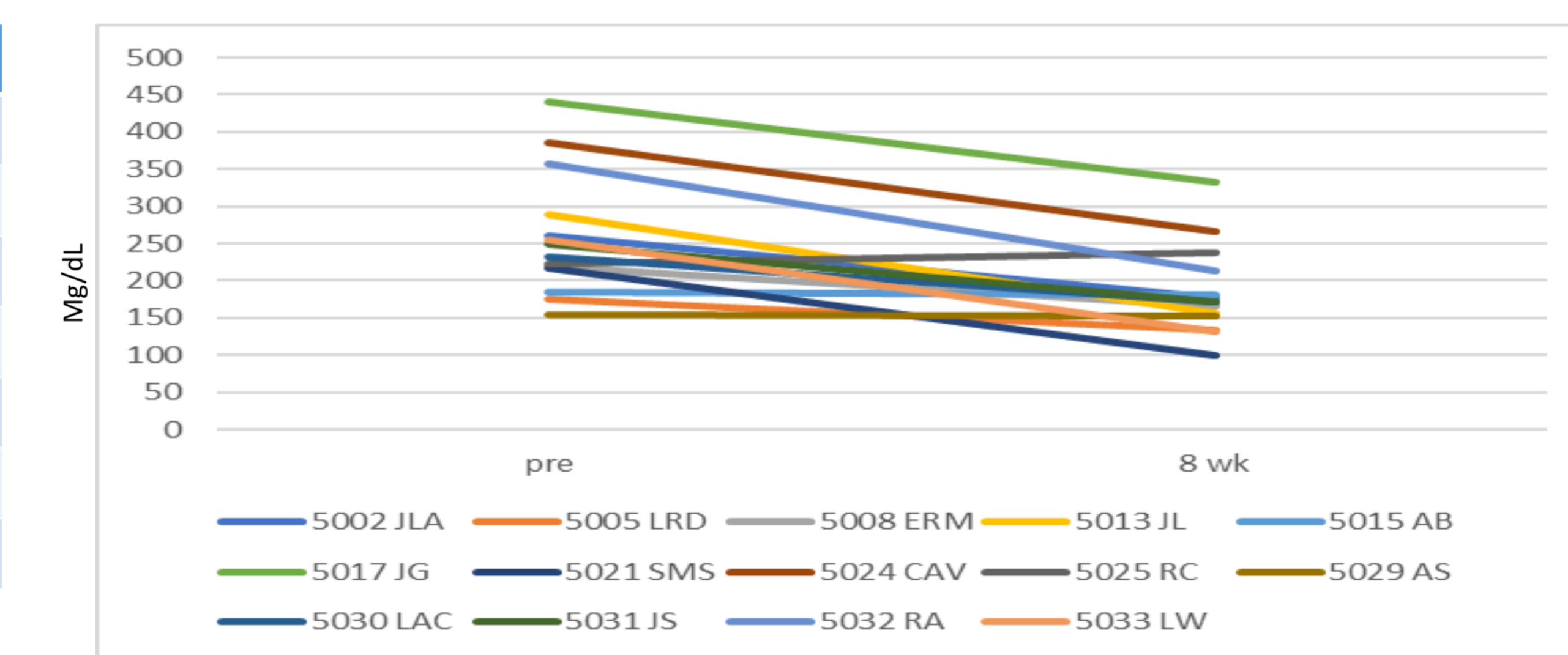
Interim Analysis without single outlier (14 Subjects)

After 8 weeks of treatment with MN-001 (tipelukast), serum triglyceride levels were reduced in 13 out of 14 subjects (Fig. 5). Pre-treatment mean serum TG was 260.1 mg/dL and post-treatment mean TG was 185.2 mg/dL. MN-001 reduced mean TG by 74.9 mg/dL, resulting in a 28.8% reduction ($p=0.00006$) (Table 3). There were no clinically significant safety and tolerability issues.

Table 3: Effects of Tipelukast on Mean Triglyceride Levels after 8 Weeks Treatment (t-test: Paired Two Sample for Means)

	pre-treatment	Week 8	Change
Mean serum TG level (mg/dL)	260.1	185.2	- 74.9 (- 28.8 %)
Variance	6796.7	3613.7	
Observations	14	14	
Pearson Correlation		0.77	
Hypothesized Mean Difference		0	
df		13	
t Stat		5.36	
P-value		0.00006	

Figure 5: Changes in Individual Subject Serum TG Levels after 8 weeks MN-001 Treatment



CONCLUSIONS

Results of the interim analysis shows that tipelukast (MN-001) demonstrates efficacy in significantly reducing mean serum TG level in NASH and NAFLD patients with hypertriglyceridemia.

Based on the results of this study, along with the results of prior clinical studies of tipelukast (MN-001) in other indications, MN-001 has the potential to benefit a wide range of patients with hypertriglyceridemia, not limited to those with NASH and NAFLD.

ACKNOWLEDGEMENTS

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CONTACT INFORMATION

Please contact Medicnova at inquiries@medicnova.com