A Phase 1 trial to evaluate the safety, PK and target engagement of MTX-463, a monoclonal antibody inhibitor of WISP1

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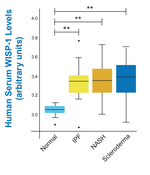
Background

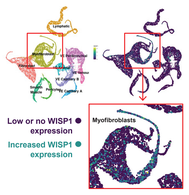
- An extracellular matrix-related protein, Wnt-inducible signaling-pathway protein 1 (WISP1) is a member of the CCN family of matricellular proteins involved in fibroblast activation and epithelial-mesenchymal crosstalk
- Increased WISP1 levels have been reported in numerous fibrotic organs, including the lung, heart, and liver[1-3]
- WISP1 levels have also been reported to be elevated in the fibrotic kidney, where levels in the sera were found to be correlated with the severity of renal fibrosis in patients with chronic kidney disease[4]
- WISP1 was shown to be highly expressed in hyperplastic ATII cells in pulmonary fibrosis, where it is postulated to mediate enhanced ATII cell proliferation and induce profibrotic gene expression. Additionally, WISP1 enhanced fibrogenesis by inducing epithelial-mesenchymal transition (EMT) of ATII cells and increasing collagen production by fibroblasts[1]
- MTX-463 is an IgG1 monoclonal antibody directed against WISP1. It is postulated that it may be effective in the treatment of IPF
- **The aim of this study** was to assess the safety, tolerability, PK, immunogenicity and target engagement of MTX-463 in a Phase 1 study in healthy individuals

WISP1 is elevated in serum of fibrotic disease patients

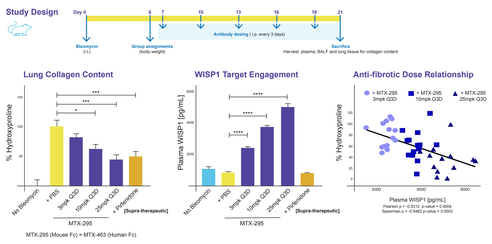


Somalogic probe WISP-1 aptamer 1 (SeqID: 13692-154). Statistical test: Kruskal-Wallis with Bonferroni correction; ** = p-value < 0.01.

WISP1 is up-regulated in myofibroblasts of IPF patients



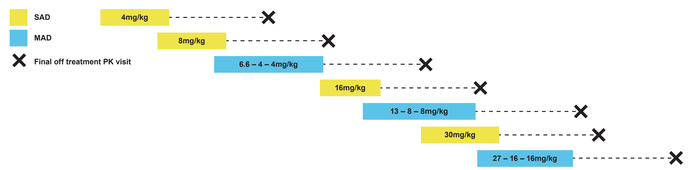
Anti-WISP1 Dose Dependently Reduces Fibrosis and Stabilizes WISP1 in a Mouse Model of Lung Fibrosis



MTX-295 (Mouse Fc) = MTX-463 (Human Fc)

Methods

- A staggered single scending / multi ascending dose (SAD / MAD) study was conducted in healthy participants
- Dose ranged from 4 mg/kg to 30 mg/kg given IV; loading doses were used in the MAD
- Each cohort had 8 participants randomized 6:2 to MTX-463 vs placebo
- Final PK blood draw 3 half lives after the final infusion



Results

Demographics

		SAD					MAD				
		4 mg/kg (N=6)	8 mg/kg (N=6)	16 mg/kg (N=6)	30 mg/kg (N=6)	Placebo (N=8)	4 mg/kg (N=6)	8 mg/kg (N=6)	16 mg/kg (N=6)	Placebo (N=8)
SEX	Female	3 (50%)	3 (50%)	2 (33.3%)	2 (33.3%)	5 (62.5%)	2 (33.3%)	2 (33.3%)	2 (33.3%)	1 (16.7%)
	Male	3 (50%)	3 (50%)	4 (66.7%)	4 (66.7%)	3 (37.5%)	4 (66.7%)	4 (66.7%)	4 (66.7%)	5 (83.3%)
ETHNICITY	Hispanic	2 (33.3%)	3 (50%)	1 (16.7%)	2 (33.3%)	4 (50%)	2 (33.3%)	0	3 (50%)	3 (50%)
	Not Hispanic	4 (66.7%)	3 (50%)	5 (83.3%)	4 (66.7%)	4(50%)	4 (66.7%)	6 (100%)	3 (50%)	3 (50%)
RACE	Native Amer	0	0	0	0	2 (25%)	0	0	1 (16.7%)	0
	Asian	0	1 (16.7%)	0	0	0	0	0	0	1 (16.7%)
	African Amer	2 (33.3%)	0	1 (16.7%)	0	0	1 (16.7%)	1 (16.7%)	1 (16.7%)	1 (16.7%)
	Pacific Isl	0	0	0	0	0	1 (16.7%)	0	0	0
	White	4 (66.7%)	5 (83.3%)	4 (66.7%)	6 (100%)	6 (75%)	4 (66.7%)	5 (83.7%)	4 (66.7%)	4 (66.7%)
	Other	0	0	1 (16.7%)	0	0	0	0	0	0
AGE	Mean (SD)	36.2 (14.70)	28.5 (8.96)	35.7 (8.12)	29.3 (11.13)	34.0 (8.73)	42.5 (11.17)	40.5 (13.29)	33.0 (6.07)	29.3 (7.03)
	Min, Max	20, 53	20, 45	28, 46	18, 48	23, 46	22, 56	29, 60	24, 40	22, 40
WEIGHT (kg)	Mean (SD)	81.03 (20.056)	76.87 (19.893)	80.88 (9.197)	69.33 (9.487)	81.24 (17.417)	80.15 (11.350)	75.50 (10.544)	73.98 (6.072)	78.57 (6.258)
	Min, Max	63.0, 112.8	53.5, 113.5	65.8, 89.8	59.0, 84.2	58.3, 112.5	61.0, 91.1	64.9, 94.0	65.2, 71.2	71.2, 88.3
BMI (kg/m²)	Mean (SD)	26.53 (4.952)	27.08 (3.540)	26.12 (0.462)	23.82 (3.828)	26.80 (3.552)	27.95 (5.582)	23.92 (2.764)	26.12 (2.144)	26.20 (2.269)
	Min, Max	22.3, 33.7	23.8, 33.9	25.6, 26.8	19.0, 28.5	21.2, 31.3	21.6, 36.7	20.5, 27.8	22.4, 28.7	23.3, 29.2
	≥30 kg/m2	2 (33%)	1 (16.7%)	0	0	2 (25%)	2 (33.3%)	0	0	0

Disposition

SAD

- 100% of all participants completed the trial as scheduled

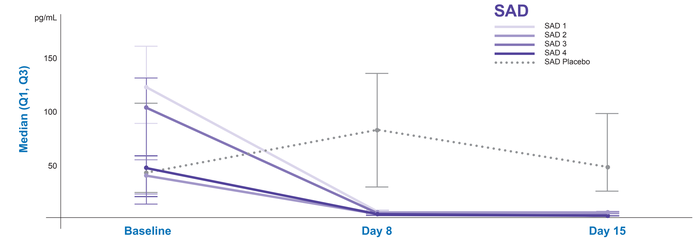
MAD

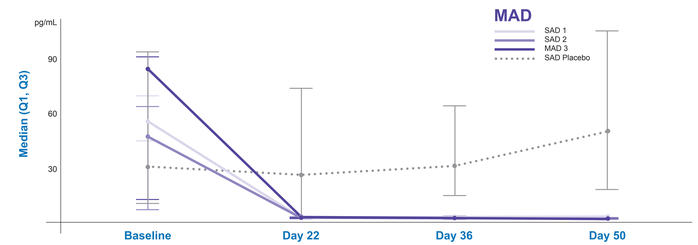
- 3 participants discontinued treatment early, 1 in each cohort
- MAD 1: a participant withdrew after all three doses but prior to final study visit due to a change in her work schedule
- MAD 2: a participant withdrew after 2 infusions due to an adverse event (pelvic pain)
- MAD 3: A participant withdrew after 1 infusion due to a change in family circumstance
- No placebo participants withdrew early

Safety

	SAD						MAD				
	4 mg/kg (N=6)	8 mg/kg (N=6)	16 mg/kg (N=6)	30 mg/kg (N=6)	All MTX-463 (N=24)	Placebo (N=8)	4 mg/kg (N=6)	8 mg/kg (N=6)	16 mg/kg (N=6)	All MTX-463 (N=18)	Placebo (N=6)
# Participants with a TEAE	1 (16.7%)	1 (16.7%)	2 (33%)	1 (16.7%)	5 (20.8%)	1 (12.5%)	0	3 (50%)	2 (33%)	5 (27.8%)	2 (33%)
# Participants with a related TEAE	0	0	1 (16.7%)	1 (16.7%)	2 (8.3%)	1 (12.5%)	0	3 (50%)	2 (33%)	5 (27.8%)	2 (33%)
# Participants with a SAE	0	0	0	0	0	0	0	0	0	0	0
# Participants with a TEAE leading to discontinuation	0	0	0	0	0	0	0	1 (16.7%)	0	1 (5.6%)	0
Highest Severity Grade Reported	2	2	2	1	2	2	NA	2	2	2	1

Target Engagement: Median Free Serum WISP1 Levels





All Reported TEAEs SAD Cohorts

	4 mg/kg (N=6)	8 mg/kg (N=6)	16 mg/kg (N=6)	30 mg/kg (N=6)	Overall Active (N=24)	Placebo (N=8)
Number of Subjects with Treatment-Emergent Adverse Events	1 (16.7%)	1 (16.7%)	2 (33.3%)	1 (16.7%)	5 (20.8%)	1 (12.5%)
Infections and infestations	0	1 (16.7%)	0	0	1 (4.2%)	0
Gastroenteritis	0	1 (16.7%)	0	0	1 (4.2%)	0
Injury, poisoning and procedural complications	1 (16.7%)	0	0	0	1 (4.2%)	0
Tooth fracture	1 (16.7%)	0	0	0	1 (4.2%)	0
Investigations	0	0	1 (16.7%)	0	1 (4.2%)	0
Muscle enzyme increased	0	0	1 (16.7%)	0	1 (4.2%)	0
Nervous system disorders	0	0	0	1 (16.7%)	1 (4.2%)	0
Headache	0	0	0	1 (16.7%)	1 (4.2%)	0
Migraine	0	0	0	1 (16.7%)	1 (4.2%)	0
Respiratory, thoracic and mediastinal disorders	0	0	1 (16.7%)	0	1 (4.2%)	0
Dyspnoea	0	0	1 (16.7%)	0	1 (4.2%)	0
Vascular disorders	0	0	1 (16.7%)	0	1 (4.2%)	0
Hot flush	0	0	1 (16.7%)	0	1 (4.2%)	0
Metabolism and nutrition disorders	0	0	0	0	0	1 (12.5%)
Hypoglycaemia	0	0	0	0	0	1 (12.5%)

All Reported TEAEs MAD Cohorts

	4 mg/kg (N=6)	8 mg/kg (N=6)	16 mg/kg (N=6)	Overall Active (N=18)	Placebo (N=6)
Number of Subjects with Treatment-Emergent Adverse Events	0	3 (50.0%)	2 (33.3%)	5 (27.8%)	2 (33.3%)
Gastrointestinal disorders	0	0	0	0	1 (16.7%)
Nausea	0	0	0	0	1 (16.7%)
Nervous system disorders	0	2 (33.33%)	0	2 (11.1%)	1 (16.7%)
Headache	0	2 (33.33%)	0	2 (11.1%)	1 (16.7%)
General disorders and administration site conditions	0	0	1 (16.7%)	1 (5.6%)	0
Injection site erythema	0	0	1 (16.7%)	1 (5.6%)	0
Infections and infestations	0	1 (16.7%)	0	1 (5.6%)	0
Viral infection	0	1 (16.7%)	0	1 (5.6%)	0
Musculoskeletal and connective tissue disorders	0	2 (33.33%)	0	2 (11.1%)	0
Back pain	0	1 (16.7%)	0	1 (5.6%)	0
Musculoskeletal chest pain	0	1 (16.7%)	0	1 (5.6%)	0
Psychiatric disorders	0	0	1 (16.7%)	1 (5.6%)	0
Depressed mood	0	0	1 (16.7%)	1 (5.6%)	0
Reproductive system and breast disorders	0	1 (16.7%)	0	1 (5.6%)	1 (12.5%)
Pelvic pain	0	1 (16.7%)	0	1 (5.6%)	1 (12.5%)

Pharmacokinetics: Summary Parameters in Healthy Adult Participants Following Repeat Infusions of MTX-463

Dose (mg/kg)	Stat. Param.	$T_{1/2}$ (day)	C_{max} (µg/mL)	C_{max}/D [(µg/mL)/(mg/kg)]	$AUC_{0\text{-}14}$ (day*µg/mL)	$AUC_{0\text{-}14}$/D [(day*µg/mL)/(mg/kg)]
4	N	6	6	6	6	6
	Mean	22.2	287	71.8	2320	579
	SD	6.74	68.8	17.2	369	92.2
	CV%	30.3	24.0	24.0	15.9	15.9
	Geo. Mean	21.4	281	70.1	2290	572
	Geo. CV%	31.2	23.4	23.4	17.5	17.5
8	N	5	5	5	5	5
	Mean	21.0	504	63.1	4030	504
	SD	5.59	90.8	11.4	1030	129
	CV%	26.6	18.0	18.0	25.6	25.6
	Geo. Mean	20.5	497	62.2	3910	488
	Geo. CV%	25.5	19.1	19.1	29.7	29.7
16	N	4	5	5	5	5
	Mean	20.0	686	42.9	6030	377
	SD	2.46	168	10.5	982	61.4
	CV%	12.3	24.5	24.5	163	163
	Geo. Mean	19.9	668	41.8	5960	373
	Geo. CV%	12.4	26.3	26.3	17.2	17.2

Immunogenicity: one anti-drug antibody (ADA) positive participant (1/42 [2.4%])

Conclusions

WISP1 is a secreted matricellular protein that appears to play an important role in fibroblast activation in IPF

MTX-463 is a monoclonal antibody inhibitor of WISP1 that appears efficacious in animal models

MTX-463 appears to be safe and well tolerated in healthy individuals

PK is linear, dose proportional and supports Q4 week IV dosing in Phase 2

Immunogenicity to MTX-463 was low (2.4%)

MTX-463 demonstrated target engagement at all doses studied

Further studies with MTX-463 in patients with IPF are warranted

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