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Pharmacokinetic and Safety Data in Monkey and Human after IV bolus Administration of MRG-106, an Inhibitor of miR-155

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Abstract

Objective:

Examine the translatability of non-human primate pharmacokinetic and safety data of MRG-106, a phosphorothioate (PS) antimiR-155 LNA/DNA mixmer oligonucleotide, using intravenous bolus injections as the route of administration to patients in a cutaneous T cell lymphoma (CTCL) Phase I clinical trial.

Methods:

PK samples were analyzed by liquid chromatography with tandem mass spectrometric detection. Safety was monitored by physical exams, clinical laboratory tests, and clinical observations and/or assessment of adverse events in non-human primates and clinical trial participants.

Results:

Preclinical studies in non-human primates (NHP) were conducted to assess the pharmacokinetics (PK) and safety of a 30 mg/kg dose of MRG-106 administered via subcutaneous (SC) injection, 2-hour IV-infusion, or 1 minute IV-bolus injection. All three routes of administration were well tolerated and had similar overall systemic exposures. The mean plasma C_{max} following IV bolus injection was 277 ± 71.2 µg/mL at the 5-minute time point (with an extrapolated C_0 of 443 ± 154 µg/mL), 7-16 fold higher than the C_{max} from SC or IV-infusion routes of administration, and 4 to 5 times higher than previously reported thresholds of plasma concentrations (50-70 µg/mL) shown to activate the complement cascade for phosphorothioate ASOs (Levin et al. 2001; Henry et al. 2008). Despite the high plasma concentrations there was no indication of clinically relevant complement activation or changes in coagulation parameters.

Based on the results from the MRG-106 study in NHPs, CTCL patients have also been dosed using SC, 2-hour IV infusion, and 1-3 minute IV bolus routes of administration. Human PK data from SC and IV infusion cohorts displayed linear kinetics, with approximately 70% bioavailability from SC dosing. Additionally, SC data compares favorably to NHP data, with similar dose normalized C_{max} and $AUC_{0\text{-}24}$ values from monkey to human (first dose C_{max} relative ratio of 1.04; $AUC_{0\text{-}24}$ relative ratio of 1.43). However, T_{max} was slightly later in patients as compared to monkeys (median T_{max} values of 1 and 3 hr, respectively). To date, MRG-106 has been well tolerated in patients at doses ranging from 300 to 900 mg per dose for SC injections and 2-hour IV infusions, and 300 mg 1-3 minute IV bolus injections (achieving a maximum C_{max} of 63.9 µg/mL).

Conclusions:

In the clinical setting, intravenous bolus administration of MRG-106 may be advantageous compared to subcutaneous or IV-infusion for patient convenience as well as potentially increasing pharmacodynamic activity. Despite overall higher tissue accumulations achieved with slow infusion, IV bolus administration of antisense oligonucleotides has been shown to result in increased pharmacodynamic activity in liver tissue, with a correlation between increased activity and higher maximal plasma concentration (Geary et al. 2009). However, despite this observation, phosphorothioate oligonucleotides are traditionally administered by subcutaneous or intravenous infusion to avoid the common, well characterized oligonucleotide class effects associated with high peak plasma concentrations such as transient prolongation of coagulation times and complement activation (Levin, 1999). With the introduction of new chemical modifications in PS oligonucleotides, including 2'-methyl, 2'-MOE, or LNA modifications, higher threshold levels for complement activation are being achieved (>100 µg/mL) (Hildebrandt-Eriksen, 2012; Henry, 2016). The data presented here shows that the phosphorothioate LNA/DNA antimiR-155 mixmer, MRG-106, may be well suited for intravenous bolus administration where high C_{max} concentrations are desired and opens the possibility of exploring the relationship between route of administration, target tissue concentrations and efficacy in the clinic.

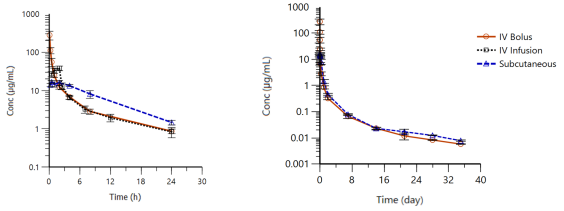
Non Human Primate Pharmacokinetic Comparison of a Single 30 mg/kg IV Bolus, IV Infusion, or Subcutaneous Dose of MRG-106

- Bi-phasic (or triphasic) plasma concentration vs time curves with short distribution phase followed by prolonged elimination phase
- Long terminal elimination half lives, representative of overall tissue elimination half-life
- High percent bioavailability $AUC_{inf,\ SC}/AUC_{inf,\ IV\ Bolus}$= 98%

Group		C_0 (µg/mL)	T_{max}* (hr)	C_{max} (µg/mL)	$AUC_{0\text{-}24}$ (µg*hr/mL)	24-hour $t_{1/2}$† (hr)	T_{last}* (day)	AUC_{inf} (µg*hr/mL)	$t_{1/2}$ (day)
IV Bolus	Mean	443	0.083	277	179	7.36	35	229	9.07
	SD	154	0	71.9	26.5	0.693	14	19.0	4.06
2-hr IV Infusion	Mean	N/A	2	37.8	125	8.79	ND	ND	ND
	SD		0	5.52	15	0.799			
Subcutaneous	Mean	N/A	1	17.1	161	6.37	35	224	9.35
	SD		1.5	1.21	7.24	0.671	21	4.02	3.84

* Median and range are shown for T_{max} and T_{last}

† Combination of distribution half-life and earlv elimination half life due to analysis being constrained to 24-hour time interval



Non Human Primate Safety Data: Single 30 mg/kg Subcutaneous or IV Bolus Dose

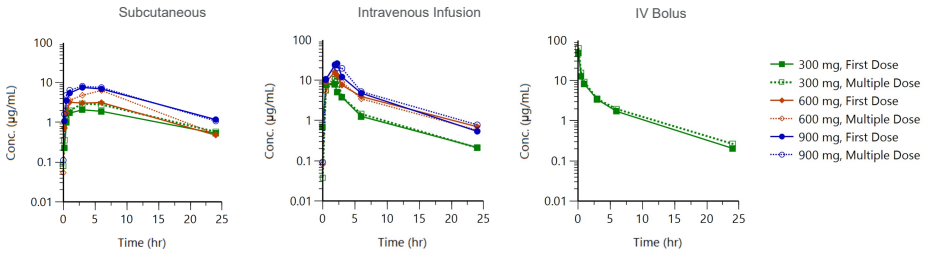
- IV bolus and subcutaneous injections were well-tolerated in non-human primates
- Transient increases of AST (4.8/4.7-fold; IV/SC), ALT (2.2/3.0-fold; IV/SC), fibrinogen (1.34/1.38-fold; IV/SC) and CK (5.0/33.8-fold; IV/SC)
- Clinical pathology findings were similar between the IV bolus and subcutaneous dosing groups,
- Increased C_{max} following IV bolus injection did not contribute to these transient effects.
- No clinically significant effects on prothrombin time (PT) or aPTT at 4 and 24 hours or 2, 7, 14, 28 and 56 days postdose compared to predose values

Group	Study Day	Mean (SD) Clinical Pathology Parameters (N=3/group)			
		AST (U/L)	ALT (U/L)	Fibrinogen (mg/dL)	Creatine Kinase (U/L)
IV bolus	-1	45 (4)	53 (24)	265 (35)	454 (154)
	2	218 (136)	114 (26)	355 (36)	2291 (747)
	7	42 (8)	63 (9)	306 (36)	264 (207)
	14	35 (4)	43 (12)	276 (22)	135 (6)
SC injection	-1	40 (6)	40 (9)	253 (32)	161 (49)
	2	190 (84)	122 (50)	348 (33)	5451 (1939)
	7	47 (8)	67 (30)	322 (57)	246 (193)
	14	41 (9)	60 (20)	308 (70)	171 (81)

- Similar changes in Bb and C5a complement split products for intravenous bolus and subcutaneous routes of administration
- Levels of increase (or decrease) in either split product is not considered to be of clinical significance for either route of administration

Group	Time Point (hr)	Bb (µg/mL)	C5a (ng/mL)
SC injection	0	2.0 (0.41)	3.9 (0.67)
	1	2.5 (0.50)	4.4 (0.20)
	24	3.1 (1.2)	5.0 (1.2)
IV bolus	0	1.6 (0.44	3.7 (0.64)
	0.083	2.8 (0.68)	4.5 (0.15)
	0.5	2.3 (0.77)	4.5 (0.56)
	24	2.8 (0.98)	4.4 (0.90)

Human Plasma Concentration vs. Time Curves and Pharmacokinetic Parameter Estimates



Dose	ROA	PK Curve	T_{max} (hr)			C_{max} (µg/mL)			$AUC_{0\text{-}24}$ (µg*hr/mL)			24-hour $t_{1/2}$ (hr)			Cl (L/hr)*			V_{ss} (L)*			V_z (L)*		
			N	Median	Range	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
300 mg	SC	First Dose	3	3	0	3	2.06	1.05	3	28.6	12.9	0			0						0		
		Multiple Dose†	3	6	3	3	3.20	0.978	3	39.3	8.56	0			0						0		
	IV Infusion	First Dose	3	1.92	1.42	3	7.83	0.347	3	34.3	8.99	3	5.45	1.22	3	8.76	2.48	3	46.6	2.10	3	66.1	6.64
		Multiple Dose	2	1.92	0	2	11.0	4.74	2	33.1	10.1	2	5.29	0.647	2	9.16	2.86	2	49.4	16.5	2	68.6	13.3
	IV Bolus	First Dose	3	0.083	0	3	48.6	7.37	3	53.1	7.51	4	5.37	0.681	3	5.54	0.812	3	27.2	4.04	4	46.4	6.24
		Multiple Dose	2	0.083	0	2	62.9	1.48	2	61.4	5.23	2	5.99	0.741	2	4.72	0.470	2	24.5	1.92	2	40.5	0.987
600 mg	SC	First Dose	3	3	5	3	3.49	0.856	3	42.7	10.6	1	8.16		1	6.62					1	78.0	
		Multiple Dose	3	6	0	3	6.33	1.27	3	68.6	17.0	0			0						0		
	IV Infusion	First Dose	3	1.92	0.33	3	16.4	2.72	3	81.7	14.9	3	6.27	1.33	3	7.00	1.54	3	50.7	2.46	3	61.3	1.58
		Multiple Dose	3	1.92	0	3	15.0	2.85	3	59.5	33.5	2	5.71	0.217	2	7.99	2.9	2	53.1	11.7	2	65.3	21.4
900 mg	SC	First Dose	3	3	0	3	7.53	1.25	3	96.0	16.0	0			0						0		
		Multiple Dose	2	4.5	3	2	8.16	1.92	2	102	22.6	0			0						0		
	IV Infusion	First Dose	3	2.25	0.33	3	29.2	6.79	3	107	24.8	3	4.97	0.350	3	8.40	1.78	3	45.1	5.70	3	59.8	10.4
		Multiple Dose	2	1.92	0	2	24.5	2.05	2	92.9	19.1	2	5.83	0.681	2	9.40	2.12	2	55.6	4.45	2	78.1	8.62

* Cl/F, Vss/F, and Vz/F for subcutaneous administration

† Samples for multiple dose PK curves were taken on Day 26, after the 6th dose.

Human to NHP C_{max} and $AUC_{0\text{-}24}$ Relative Ratios

ROA	C_{max} RR	$AUC_{0\text{-}24}$RR
Subcutaneous	1.04	1.43
IV Infusion	2.06	2.62
IV Bolus	1.28	2.17

- Relative ratios based on mg/kg normalization scale well for subcutaneous dosing between NHP and human, but requires approximately 2-fold scaling for IV routes of administration

Human Dose Normalized C_{max} and $AUC_{0\text{-}24}$

ROA	Dose (mg)	Mean C_{max}/Dose (SD) (ng/mL/mg)		Mean $AUC_{0\text{-}24}$/Dose (SD) (ng*hr/mL/mg)	
		First Dose	Multiple Dose	First Dose	Multiple Dose
SC	300	6.88 (3.50)	10.7 (3.26)	95.4 (43.2)	131 (28.5)
	600	5.82 (1.43)	10.5 (2.12)	71.2 (17.7)	114 (28.3)
	900	8.36 (1.39)	9.07	96.6	113
IV Infusion	300	26.1 (1.16)	36.5	114 (30.0)	110
	600	27.3 (4.54)	24.9 (4.76)	136 (24.9)	99.2 (55.8)
	900	32.4 (7.54)	27.2	119 (27.6)	103

Human Plasma Trough Concentrations After Extended Dosing

- Predose samples collected on Day 1 of each 28-Day cycle, with 1x per week dosing

Dose	Subject	ROA	Trough Plasma Concentration (ng/mL)							
			C1	C2	C3	C4	C5	C6	C7	C8
300 mg	101-004	IV Bolus	36.6							
	102-007	IV Infusion	31.5	38.4	50.0	49.3	49.8	42.7		
	107-003	IV Infusion	195	900	2330	Pending	6430	6090	6710	
600 mg	102-005	SC	BLOQ	52.7	52.2	81.4	79.3	99.0	92.9	74.8
	102-008	IV Infusion	81.9	109	124	162	264			
	102-009	IV Infusion	35.4	55.7	90.2	94.3				
900 mg	105-003	SC	70.5	79.9	126	202	175	243	238	201
	106-002	SC	45.0	78.6						
	112-004	IV Infusion	88.2	84.4						

- Plasma trough concentrations increase in an approximate dose proportional manner
- Steady state reached after 3-4 cycles (~3-4 months) of regular dosing, indicative of long tissue half lives
- Subject 107-003 trough concentrations indicate accumulation of MRG-106 despite normal safety labs and renal function tests.

Conclusions

- Plasma concentration curves are multi-compartmental with 2 or 3 phases
- IV bolus dosing of up to 30 mg/kg in non human primates was well tolerated, reaching a C_{max} of 277 µg/mL
- No adverse effects on coagulation, complement activation, or clinical chemistry parameters were observed as a result of IV bolus dosing in NHP
- MRG-106 is well tolerated when administered via subcutaneous injection, intravenous infusion, or intravenous bolus injection in human subjects
- Maximum achieved C_{max} in human subjects is 63.9 µg/mL (IV bolus)
- MRG-106 displays linear kinetics, with dose proportional increases in C_{max} and AUC across dose groups
- High percent bioavailability observed for subcutaneous dosing
- No evidence of accumulation at the highest doses tested for any route of administration
- Relative ratios between monkey and man scaled by mg/kg dosing are appropriate for subcutaneous dosing
- Plasma trough values after extended twice weekly dosing scale proportional to dose and reach steady state after 3-4 months of dosing

References

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ClinicalTrials.gov Identifier: NCT02580552

Disclosure

Authors of this presentation have the following to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation:

Brent Dickinson, Linda Pestano, Anita Seto, Judy Ruckman, Michele Landry, Mark Sanseverino, Ioanna Paxton, Robert Hopkins, Gilad Gordon, Paul Rubin, and William Marshall are employees or consultants of miRagen Therapeutics, Inc.

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