Toxicokinetics of NIDO-361, a Potential Candidate to Treat Spinal and Bulbar Muscular Atrophy (SBMA), in Rats and Monkeys Following Oral Dosing in a 4-Week Toxicity Study

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POSTER # LP-59

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PURPOSE

While the underlying genetic causes of many rare diseases have been elucidated, there is still a gap between understanding disease conditions and translating this knowledge to effective treatments. In most circumstances, rare diseases have no cure and limited options for therapeutic intervention. Therefore, supporting advancement of rare disease drug programs through rigorous design of preclinical studies combined with analytical assessment of study outcomes is crucial in addressing this ongoing global health issue.

NIDO-361 is a novel small molecule that binds to a distinct site on the androgen receptor (AR) to regulate co-factor binding and thereby corrects transcriptional dysregulation. NIDO-361 is currently being investigated for the treatment of patients suffering from Spinal and Bulbar Muscular Atrophy (SBMA); a rare inherited X-linked neuromuscular disorder caused by a genetic mutation of the AR resulting in the loss of skeletal muscle and motor neuron function. In this study, the toxicokinetics (TK) of NIDO-361 was assessed following once-daily oral dosing to male Sprague Dawley rats and male Cynomolgus monkeys. Analysis of NIDO-361 plasma concentrations was performed by HPLC/MS/MS and the resulting data sets were used to evaluate the drug exposure profile and to inform dosing decisions for future studies.

STUDY DESIGN

For the rat study, animals received once-daily oral dosing of NIDO-361 as follows:

- **Group 1 – N=3, 0 mg/kg/day (control) for 28d**
- **Group 2 – N=6, 25 mg/kg/day for 28d**
- **Group 3 – N=6, 100 mg/kg/day for 28d**
- **Group 4 – N=10, 250 mg/kg/day for 4d, no dosing D5-D7, 150 mg/kg/day D8-D28**

For the monkey study, animals received once-daily oral dosing of NIDO-361 as follows:

- **Group 1 – N=7, 0 mg/kg/day (control) for 28d**
- **Group 2 – N=4, 45 mg/kg/day for 28d**
- **Group 3 – N=7, 200 mg/kg/day, reduced to 100 mg/kg/day on D5**
- **Group 4 – N=7, 600 mg/kg/day, dosing stopped on D5**

Blood samples were collected at predetermined times from 3 rats/timepoint and all surviving monkeys on D1 and D28. NIDO-361 plasma concentrations were measured by validated HPLC/MS/MS methods. TK parameters were determined by model independent methods (sparse sampling for the rat study, serial sampling for the monkey study).

RESULTS

Day 1 NIDO-361 TK in Rats

Following a single oral administration of NIDO-361 at 25, 100, 150 and 250 mg/kg/day to male rats, NIDO-361 was absorbed into the systemic circulation with T_{max} values ranging from 1.00 to 24.0 h post dose. NIDO-361 C_{max} values were 2,250, 6,770, 7,030 and 12,800 ng/mL and the $AUC_{(0-24)}$ values were 14,300, 108,000, 107,000 and 212,000 ng·h/mL for doses of 25, 100, 150 and 250 mg/kg/day, respectively (Table 1). NIDO-361 systemic exposure (C_{max} and $AUC_{(0-24)}$) increased with increasing dose in an approximately dose proportional manner (Table 1, Figure 1).

Day 28 NIDO-361 TK in Rats

Day 28 NIDO-361 C_{max} values were 1,670, 8,280 and 12,300 ng/mL and the $AUC_{(0-24)}$ values were 10,100, 123,000 and 175,000 ng·h/mL for doses of 25, 100 and 150 mg/kg/day, respectively (Table 1). C_{max} values of NIDO-361 increased in an approximately dose proportional manner from 25 to 150 mg/kg/day, while $AUC_{(0-24)}$ values of NIDO-361 were generally not proportional to dose across the entire dose range (Table 1 and Figure 1). Day 28/Day 1 NIDO-361 C_{max} ratios were 0.742, 1.22 and 1.74 and the Day 28/Day 1 NIDO-361 $AUC_{(0-24)}$ ratios were 0.710, 1.13 and 1.64 for doses of 25, 100 and 150 mg/kg/day, respectively (Table 1). Day 28 overall TK exposure was similar to that of Day 1.

Day 1 NIDO-361 TK in Monkeys

Following a single oral administration of NIDO-361 at 45, 200 and 600 mg/kg/day to male monkeys, NIDO-361 was absorbed into the systemic circulation with T_{max} values ranging from 2.00 to 8.00 h post dose (Table 2). Mean C_{max} values were 6,460, 12,600 and 19,900 ng/mL and the mean $AUC_{(0-24)}$ values were 119,000, 246,000 and 384,000 ng·h/mL for NIDO-361 doses of 45, 200 and 600 mg/kg/day, respectively (Table 2). NIDO-361 systemic exposure (C_{max} and $AUC_{(0-24)}$) increased with increasing dose in an approximately dose proportional manner (Table 2 and Figure 2).

Day 28 NIDO-361 TK in Monkeys

Day 28 mean C_{max} values were 8,630 and 17,800 ng/mL and the mean $AUC_{(0-24)}$ values were 160,000 and 298,000 ng·h/mL for NIDO-361 doses of 45 and 100 mg/kg/day, respectively (Table 1). Systemic exposure of NIDO-361 increased with dose in an approximately dose proportional manner. The Day 28 C_{max} and $AUC_{(0-24)}$ values of NIDO-361 at 45 mg/kg/day were similar to Day 1 values. Day 28/Day 1 C_{max} and $AUC_{(0-24)}$ ratios were 1.34 and 1.35, respectively, at 45 mg/kg/day (Table 2).

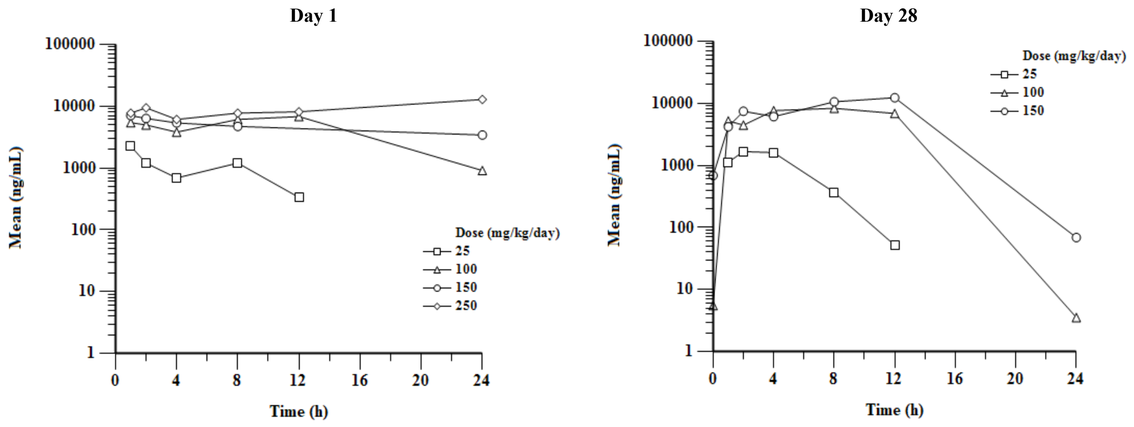

Figure 1: Mean Plasma Concentration-Time Profiles of NIDO-361 in Male Rats Following Once Daily Oral Administration of NIDO-361 for 28 Days (semi-logarithmic scale)

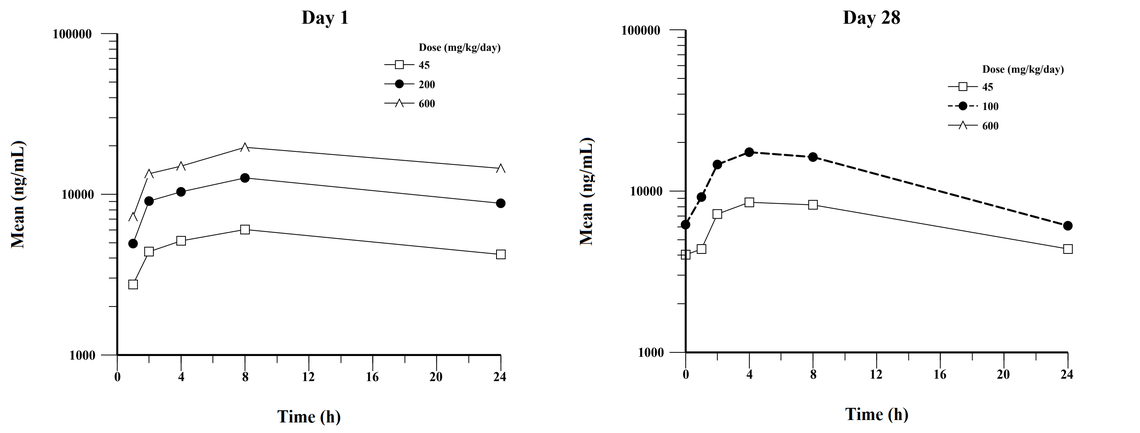

Figure 2: Mean Plasma Concentration-Time Profiles of NIDO-361 in Male Monkeys Following Once Daily Oral Administration of NIDO-361 for 28 Days (semi-logarithmic scale)

		Rats						
Parameter	**Units**	**Day 1**				**Day 28**		
Dose	***mg/kg/day***	**25**	**100**	**150[a]**	**250**	**25**	**100**	**150**
T_{max}	*h*	1.00	12.0	1.00	24.0	2.00	8.00	12.0
C_{max}	*ng/mL*	2,250	6,770	7,030	12,800	1,670	8,280	12,300
C_{max}/Dose	*ng/mL/(mg/kg)*	90.0	67.7	46.9	51.2	66.8	82.8	82.0
T_{last}	*H*	12.0	24.0	24.0	24.0	12.0	24.0	24.0
$AUC_{(0-T)}$	*ng·h/mL*	11,600	108,000	107,000	212,000	10,000	123,000	175,000
$AUC_{(0-T)}$/Dose	*ng·h/mL/(mg/kg)*	464	1,080	713	848	400	1,230	1,170
$AUC_{(0-24)}$	*ng·h/mL*	14,300	108,000	107,000	212,000	10,100	123,000	175,000
$AUC_{(0-24)}$/Dose	*ng·h/mL/(mg/kg)*	572	1,080	713	848	404	1,230	1,170
C_{max}	*Day 28/Day 1 Ratio*	-	-	-	-	0.742	1.22	1.74
$AUC_{(0-24)}$	*Day 28/Day 1 Ratio*	-	-	-	-	0.710	1.13	1.64

Table 1. Plasma TK Parameters of NIDO-361 in Male Rats Following Once Daily Oral Administration of NIDO-361 for 28 days ([a] the first day of dosing for the 150 mg/kg/day dose group was on Day 8 and was treated as Day 1 for the purpose of conducting the TK analysis)

		Monkeys				
Parameter	**Units**	**Day 1**			**Day 28**	
Dose	***mg/kg/day***	**45**	**200**	**600**	**45**	**100**
T_{max}	*h*	6.50	7.43	10.3	5.00	4.67
C_{max}	*ng/mL*	6,460	12,600	19,900	8,630	17,800
C_{max}/Dose	*ng/mL/(mg/kg)*	144	63.3	33.2	192	178
T_{last}	*H*	24.0	24.0	24.0	24.0	24.0
$AUC_{(0-T)}$	*ng·h/mL*	-	-	-	-	-
$AUC_{(0-T)}$/Dose	*ng·h/mL/(mg/kg)*	-	-	-	-	-
$AUC_{(0-24)}$	*ng·h/mL*	119,000	246,000	384,000	160,000	298,000
$AUC_{(0-24)}$/Dose	*ng·h/mL/(mg/kg)*	2,640	1,230	641	192	2,980
C_{max}	*Day 28/Day 1 Ratio*	-	-	-	1.34	-
$AUC_{(0-24)}$	*Day 28/Day 1 Ratio*	-	-	-	1.35	-

Table 2. Plasma TK Parameters of NIDO-361 in Male Monkeys Following Once Daily Oral Administration of NIDO-361 for 28 days

CONCLUSIONS

Following the completion of the outlined studies for both rat and monkey, the samples collected from animals on D1 and D28 were analyzed and the plasma concentrations of NIDO-361 quantitated. Tmax, Cmax, and AUC(0-24) values were calculated and the systemic exposure of NIDO-361 determined. For all dosed groups in the rat and monkey studies, D28 TK exposure was generally comparable to that of D1. NIDO-361 systemic exposure (Cmax and AUC(0-24)) displayed dose proportional increases with increasing dose.

Overall, the pattern of NIDO-361 systemic exposure in treated animals appeared to be similar in both species, where the systemic exposure increased in an approximately dose proportional manner and exhibited no accumulation. Measuring the potential toxicity of NIDO-361 in relation to dose was a critical step in understanding the drug's exposure profile and provided key information for dosing decisions prior to first-in-human studies.

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