Intrathecal Administration Techniques for CNS Delivery in Non-Human Primates: Practical Tools for Oligonucleotide Drug Pharmacokinetics

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Introduction

The intrathecal administration technique provides a promising route for delivering drug candidates, overcoming biological barriers, and enhancing therapeutic efficacy in treating central nervous system (CNS) diseases. However, the commonly used intrathecal (IT) administration via lumbar puncture in non-human primates often results in a low success rate and inconsistent data, which pose challenges for CNS drug development. Given the significant difficulty posed by the blood-brain barrier (BBB) for oligonucleotide drugs to penetrate into the CNS, we sought to address these issues by developing a dual catheter-port system model. This model employs one lumbar catheter-port for dose administration and another cisterna magna catheter-port for repeated cerebrospinal fluid (CSF) sampling.

Our findings indicate that the dual catheter-port system in non-human primates achieved a 100% success rate in both drug administration and CSF sampling. This technique provides a more reliable and consistent approach for pharmacokinetic studies of oligonucleotide drug candidates.

Methods

2.1. Dual Catheter-port System in Cynomolgus Monkeys (Figure 1)

Catheter Configuration

- Lumbar catheter: Drug administration (Inserted between L4 and L7)
- Cisterna magna catheter: CSF sampling

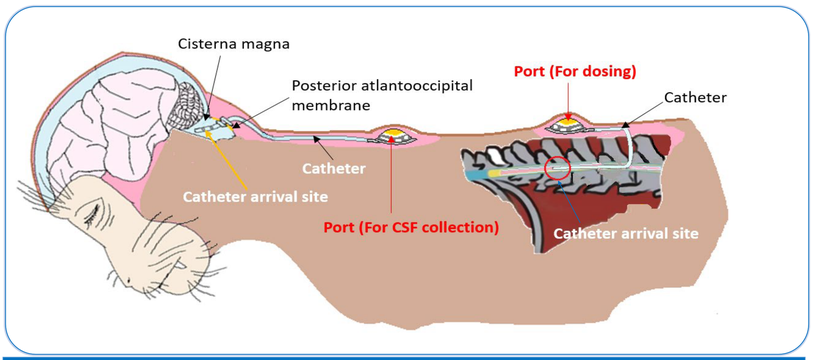

Figure 1. Dual lumbar and cistern magna intrathecal catheter-port system

2.2. Three-Phase Nusinersen Dosing Design (Detailed in Table 1)

- Test Article: Nusinersen sodium
- LC-MS/MS-SCIEX Triple Quad™ 6500
- Variable volumes/rates to assess CSF distribution kinetics

Table 1. Three-Phase Nusinersen Dosing Design for IT bolus Validation

Test Article	Dosage (mg/animal)	Phase	IT Route	Volume (mL)	Rate (mL/min)	Duration (min)	CSF sampling (h)	Blood sampling (h)
Nusinersen	1	1	infusion	2	0.5	4	0.25, 1, 6, 24	0.25, 1, 2, 6, 8, 24
		7 days washout period						
		2	infusion	1	0.5	2		
		7 days washout period						
		3	bolus	1	NA	< 0.5		

Results

Table 2. PK Result in Plasma and CSF

IT-Phase1				
Plasma concentration (ng/mL)				
Time (h)	C1501	C1502	C1503	Mean
0.25	BQL	BQL	BQL	ND
1	BQL	BQL	22.4	ND
2	24.5	27.7	42.5	31.6
6	64.1	95.9	134	98.0
8	74.3	48.9	68.8	64.0
24	BQL	BQL	BQL	ND
CSF concentration (ng/mL)				
Time (h)	C1501	C1502	C1503	Mean
0.25	189000	107000	180000	158667
1	112000	79700	103000	98233
6	21800	20300	25100	22400
24	2890	4170	2520	3193

IT-Phase2				
Plasma concentration (ng/mL)				
Time (h)	C1501	C1502	C1503	Mean
0.25	BQL	BQL	BQL	ND
1	BQL	30.1	BQL	ND
2	23.0	56.4	24.0	34.5
6	77.1	110	116	101
8	72.3	67.7	73.4	71.1
24	BQL	BQL	BQL	ND
CSF concentration (ng/mL)				
Time (h)	C1501	C1502	C1503	Mean
0.25	99900	200000	165000	154967
1	72600	86400	95500	84833
6	28700	11700	23600	21333
24	6590	788	3070	3483

IT-Phase3				
Plasma concentration (ng/mL)				
Time (h)	C1501	C1502	C1503	Mean
0.25	BQL	BQL	BQL	ND
1	BQL	31.4	20.3	25.9
2	20.9	54.8	25.2	33.6
6	62.6	106	94.3	87.6
8	63.0	72.5	83.9	73.1
24	BQL	BQL	BQL	ND
CSF concentration (ng/mL)				
Time (h)	C1501	C1502	C1503	Mean
0.25	173000	186000	176000	178333
1	83800	109000	93700	95500
6	21400	16500	20500	19467
24	2940	1170	2410	2173

■**Criteria for Successful Administration:** The total circulation CSF volume for a monkey is ~15 milliliters, and the CSF circulation is a closed system. The dose level divided by 15 mL represents theoretical maximum concentration (TMC). Dosing is considered successful when the highest concentration (initial concentration) divided by the TMC exceeds 25%.

■**Take a ASO IT administration for example**, The TMC is 0.07mg/mL (1 mg in 15 mL), and 25% of TMC is 0.017 mg/mL, which is regarded as the threshold. Achieving an initial CSF concentration of threshold (17000 ng/mL) or higher at 0.25 hour is considered successful.

The results from Table 2 and Table 3 demonstrate that Nusinersen achieves substantial CSF exposure using the IT catheter-port model (1 mg fixed dose). Furthermore, Nusinersen concentrations in the CSF were significantly higher than those in the blood, with the CSF AUC being several orders of magnitude greater than the plasma AUC.

Table 3. Three-Phase Review of Nusinersen CSF PK parameters in monkeys after IT bolus dose

Nusinersen AUC(h.ug/mL) in CSF						
1mg/animal	Animal 1	Animal 2	Animal 3	Average	Mean±SD	（Mean±SD）*3
Phase 1	578	483.5	578.6	546.7	546.7±54.8	1640.1±164.4
Phase 2	583.6	386.1	554.3	508	508.0±106.6	1524.0±319.8
Phase 3	509.9	480.6	512.9	501.1	501.1±17.9	1503.3±53.7

Table 4. Review of Nusinersen[1]CSF PK parameters in adult monkeys after IT bolus dose

Dose Level	Variable	Units	N	Mean ± SD	Median (Range)
3 mg/animal	AUC	hr*μg/mL	8	1641 ± 758	1425 (977 - 3159)

Table 2 Analysis:

► IT administration robustness confirmed – CSF exposure remains consistent across all three study phases:

• Variations in dose volume and differences in dose rate, inter-phase CV < 5% for AUC

► Cross-study Validation (Table 3 vs Table 4)

Overall study mean AUC aligns with FDA filing data. CV is lower than the FDA filing data.

Conclusion

- Our validation study supports the reliability and effectiveness of the intrathecal catheter-port system for delivering and sampling Nusinersen in non-human primates. We achieved a 100% success rate in drug administration and sampling across multiple phases, with the system maintaining consistent CSF exposure levels under varying dosing volumes and administration rates.
- The validation data showed greater consistency within the same phase compared to FDA filing data, enhancing data comparability. Additionally, in formal pharmacokinetic studies conducted for clients, a 100% success rate in dosing and sampling was achieved, with consistently reliable data obtained in over 100 monkeys.

References

[1] Nusinersen FDA Pharmacology Review

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