Spherical Nucleic Acids Show Increased Distribution and Longer Persistence than Linear Oligonucleotides in Rat Brain Following IT Administration

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OBJECTIVE

Compare and characterize the pharmacokinetics and central nervous system distribution of intrathecally (IT) administered nusinersen and nusinersen-SNA using single-photon emission computed tomography combined with computed tomography (SPECT/CT) in rats.

METHODS

125I-labeled nusinersen-SNA and nusinersen were injected IT into Sprague Dawley rats as a single 70μL bolus emulsion containing 190 to 375μCi of radioactivity.

Animals were imaged by SPECT/CT at 0-1, 24, 72, and 168 hours (hr) after dosing.

Animals were sacrificed after the final (168 hr) time point and whole brain was drawn from cardiac puncture (up to 6 mL) for gamma counting in blood and plasma.

Whole-body field of view imaging was used with feet first/prone positioning for both SPECT and CT.

SPECT scans were acquired in 4 × 9 minute frames for the 0-1 hr time points, and in 1 × 30 minute frames for the 24, 72, and 168 hr time points.

Regions of interest were defined using VivoQuant (invicro, LLC). A 13-region rat brain atlas was placed onto each image, and radioactivity signals were decay-corrected from the time of measurement to the time of injection.

CONCLUSIONS

• Immediate and pronounced CNS distribution, particularly in the spinal cord, was observed in both nusinersen and nusinersen-SNA IT injected rats.

• Nusinersen-SNA persists throughout the CNS, including in the brain and spinal cord, longer than nusinersen. These results explain, at least in part, our previous observations that nusinersen-SNA improves survival duration of SMA mice after a single injection.

• In line with these findings, the presence of nusinersen in the kidneys was significantly increased at 6, 24, 72, and 168 hours relative to nusinersen-SNA.

• Subsequent studies are currently investigating the CNS biodistribution of nusinersen and nusinersen-SNA in non-human primates at comparable and extended time points.

• Collectively, these data strongly support the therapeutic potential of SNAs for treating CNS disorders.