AWARD NUMBER: W81XWH-18-1-0165

TITLE: Development of a Splice-Switching Antisense Oligonucleotide for the Treatment of Spinal Muscular Atrophy

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TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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5b. GRANT NUMBER

W81XWH-18-1-0165

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
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13. SUPPLEMENTARY NOTES

14. **ABSTRACT:**

Determine how long SMN protein levels are elevated in E1v1.11 treated mice analyzed via SMN ELISA assay. These samples were collected in early 2020 and analyzed via ELISA by a vendor. Due to processing complications, some of these samples need to be verified, which was to be initiated in March 2020 but halted due to the campus-wide shutdown because of Covid-19. This shutdown slowed and nearly stopped research capabilities for several months. These studies are now ongoing following university policies in regards to Covid-safe access protocols.

15. SUBJECT TERMS

NONE LISTED

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	23	19b. TELEPHONE NUMBER *(include area code)*

Accomplishments:

Aim 1: Completed

Aim 2: Assay development and analysis is in progress.

Determine how long SMN protein levels are elevated in E1$^{v1.11}$ treated mice analyzed via SMN ELISA assay. These samples were collected in early 2020 and analyzed via ELISA by a vendor. Due to processing complications, some of these samples need to be verified, which was to be initiated in March 2020 but halted due to the campus-wide shutdown because of Covid-19. This shutdown slowed and nearly stopped research capabilities for several months. These studies are now ongoing following university policies in regards to Covid-safe access protocols.

Aim 3: Perform preliminary pharmacokinetics/toxicity studie

i) E1$^{v1.11}$ Toxicity Studies in Juvenile CD-1 Mice (single dose, 2-week recovery)

Shift conducted a series of three experiments in newborn CD-1 mice with single-doses (0, 13, 27, 134, 670, 1340 and 2000 μg) of ICV administered E1$^{v1.11}$. The following parameters were evaluated:

- Clinical observations: behavior, body and organ weights
- Clinical pathology: full blood workup (Hematology and Clinical Chemistry)
- Histopathology: brain, spinal cord, liver, kidney, heart, etc.
- All pathology was performed by licensed medical pathologists

Newborn CD-1 mice were randomly selected at birth and received a single ICV injection on post-natal day 2 with 2 mg being administered in two 1 mg doses approximately 8 hours apart. Mice were allowed to recover for 14 days post-injection; animals were harvested for blood analysis and tissue samples.

Quotes from Clinical Pathology Reports:

"Most of the observed changes were of negligible magnitude, sporadic in nature and consistent with biologic variation. Overall, no test article related changes are observed."

- Clinical Chemistry Final Report: Charles E. Wiedmeyer DVM, PhD, DACVP, Comparative Clinical Pathology Services

"*No treatment related histological findings were detected in the tissues examined. No adverse drug effects were noted*."

- Pathologist, Jennifer Hughes, DVM, MS, MicroCorps Pathology Services

CD-1 Toxicity Results Summary:

- No acute deaths or drug-related deaths occurred throughout the study
- Mouse growth and weight gain occurred at similar rates throughout the dose range
- Minimal differences were observed between male and female subjects
- There were no lack of movement, abnormal activity, or hunched posture observed in any of the individual mice. Additionally, all mice were responsive and did not show signs of dehydration.
- All tissue samples appeared acceptable with no effects noted due to drug dosing (**Figure 1**)
- All blood work showed no effective change noted across the dose range (**Figure 2**)

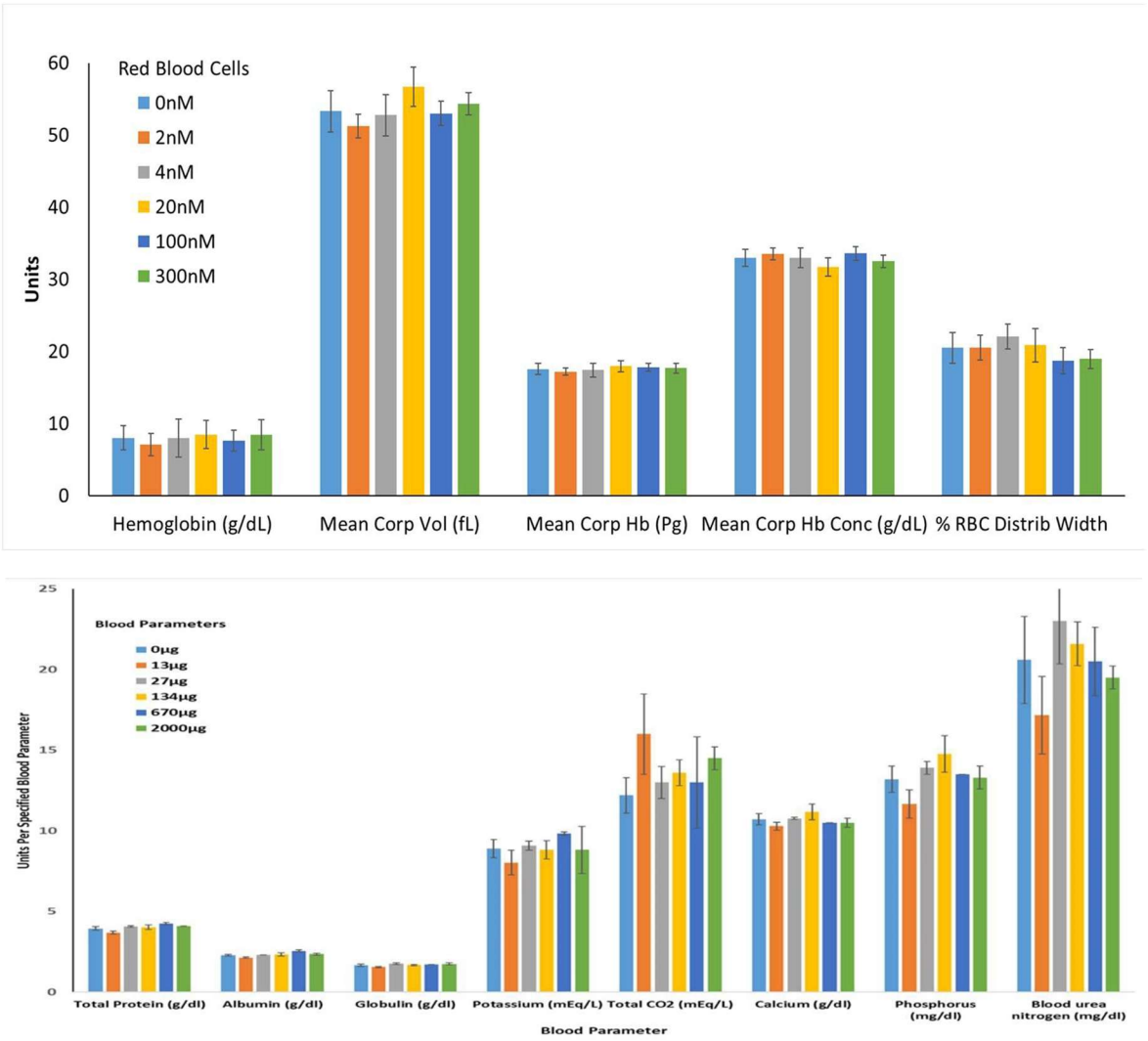


Figure 1: Representative CBC and blood chemistry results across dosing range for preliminary toxicity studies. Blood was collected 14-days post injection (unpublished data).

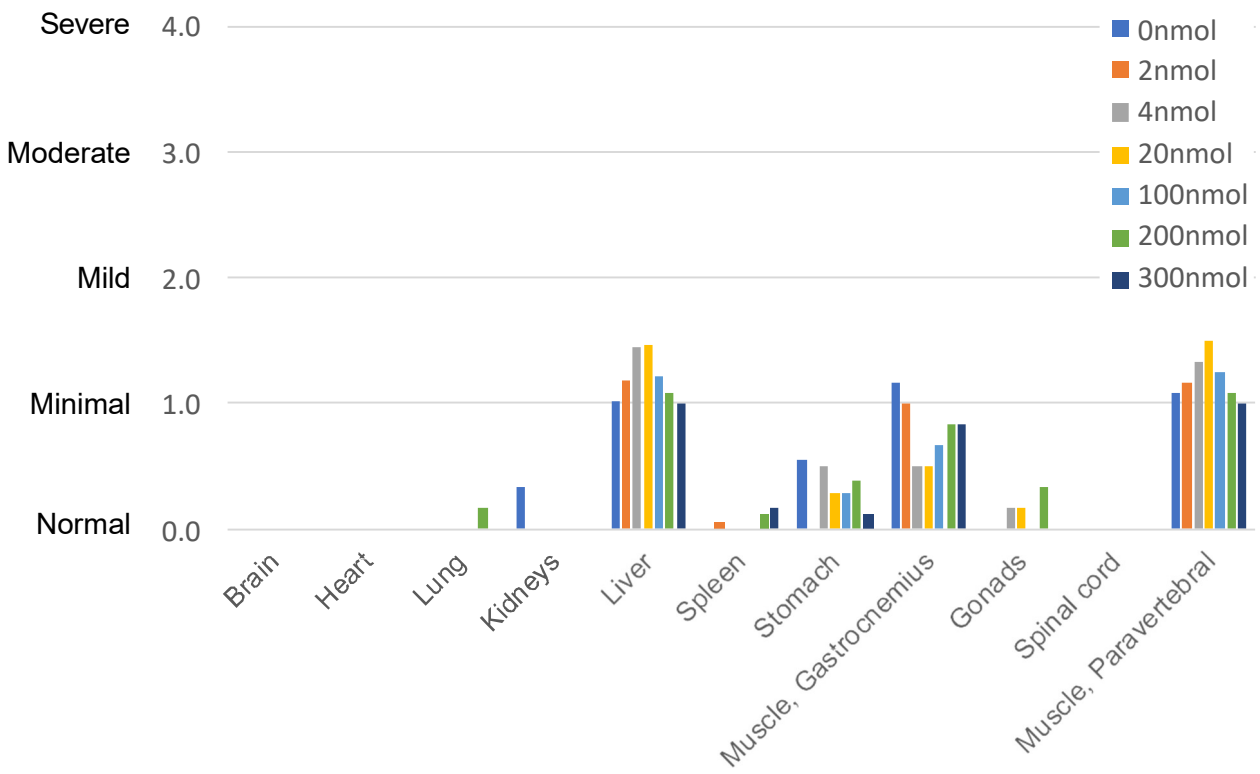


Figure 2: Histology severity scores rated by tissue type and dosing in CD-1 mice. Tissues were scored base on a 4 point scale. Certain tissues (brain, heart, etc) received all "0.0" scores, but are included in the graph (unpublished data).

Additional Toxicity/Safety Studies

During this reporting period, **all SD rat toxicity studies (adult and juvenile) were completed and analyzed according to the following basic study design (Figure 3):**

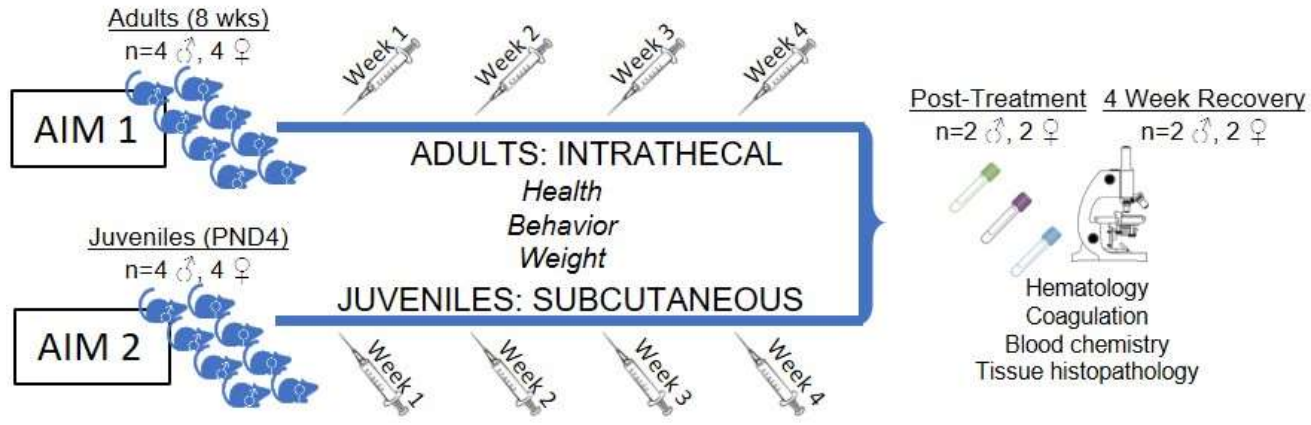


Figure 3: **Phase 1 SD Rat Study Design.** Adult SD and juvenile SD rats received weekly injections and analysis

All animals were analyzed for clinical observations of behavior, ambulation, and body weights, Clinical pathology consisting of CBC: complete blood count including the following parameters: WBC (white blood cell count), RBC (red blood cell count), HGB (hemoglobin), HCT (hematocrit), MCV (mean corpuscular volume), MCH (mean corpuscular hemoglobin), MCHC (mean corpuscular hemoglobin concentration), RDW-CV (red blood cell distribution width), Retic (reticulocyte count), platelet count, segmented neutrophil count, banded neutrophil count, lymphocyte count, monocyte count, eosinophil count, basophil count, nucleated red blood cell count and morphology, chemistry panel including: ALP (alkaline phosphatase), AST (aspartate
aminotransferase), ALT (alanine aminotransferase), CK (creatine kinase), albumin, total bilirubin, bilirubin-conjugated, bilirubin-unconjugated, total protein, globulin, BUN (blood urea nitrogen), creatinine, cholesterol, glucose, calcium, phosphorus, bicarbonate, chloride, potassium, sodium and coagulation panel including: PT (prothrombin time), PTT (partial thromboplastin time) and fibrinogen. Histopathology was performed by boarded veterinary pathologist on: brain, spinal cord, dorsal root ganglia, liver, kidney, heart, lung, and muscle.

RESULTS:

All animals survived and remained healthy through the study period, gaining weight at similar rates throughout all dose ranges. All adults recovered smoothly, rapidly and without complication from each anesthetic episode/injection. Adults showed no immediate or delayed ambulatory, behavioral or neurological defects from the lumbar intrathecal injection procedure. Juvenile rats showed normal neonatal/juvenile behavior as compared to untreated littermates and were accepted by their dams for a normal suckling period and weaned without complication. All animals gained weight as expected with no significant differences between control and treatment groups throughout the study timeframe (Figure 4).

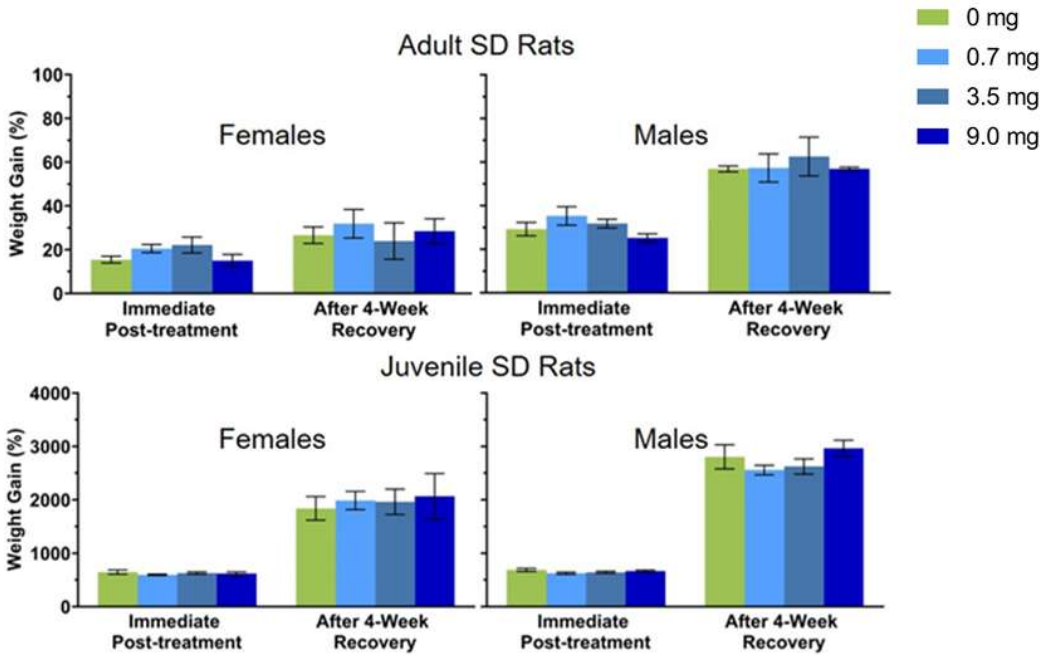


Figure 4: Overall Percent Weight Gain in Repeat-Dose Safety Studies with E1[v1.11]. Data represented are mean plus SEM. One-way ANOVA with Tukey's post-hoc shows no statistical difference between adult groups on Day 22 (n=8, weights are at time of final dose) and on day 51 (n=4, weights are following four-week recovery period), and no statistical difference between juvenile groups on post-natal day 25 (n=8, weights are at time of final dose) and on day 53 (n=4, weights are following four-week recovery period). p-values are all >0.05.

Clinical Pathology Findings:

Hematology and blood chemistry results aligned with previously performed mouse studies as **all** rats showed **normal blood urea nitrogen (BUN), creatinine, alkaline phosphatase (ALKP), and alanine aminotransferase (ALT), indicating normal renal and hepatic function**. Importantly, as increases in partial thromboplastin time (PTT) has been noted in previously reported ASO studies (Biogen/Ionis), **we thoroughly evaluated coagulation profiles and saw no elevations in prothrombin time (PT) or PTT and no differences between treatment groups. Likewise, platelets in all dosing groups appeared unaffected by drug.** When evaluating all clinical pathology findings, elevation in AST (p=0.0478) with simultaneous elevation in CK in two immediate post-treatment animals was determined to be indicative of inadvertent muscle injury during the lumbar injection procedure (8). Hepatic injury was ruled out in these

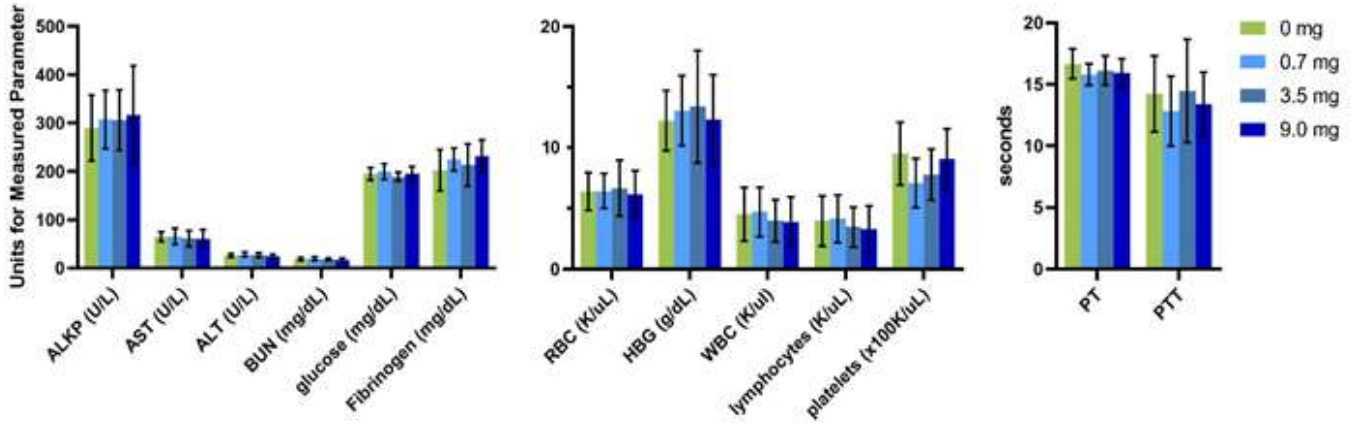


Figure 5: Figure 5: Compiled chemistry, hematology and coagulation panel data from all juvenile animals (n=8). One-way ANOVA with Dunnett's post hoc reveals no significant difference (P>0.05) between all groups. A subset of the tests performed are shown in Figure 5 for brevity. All clinical pathology findings showed no statistical differences between dosing groups.

animals by observing that other key liver enzymes (ALKP and ALT), as well as total bilirubin and liver anatomic histopathology (noted in the next paragraph) were normal. Additionally, AST and CK were normal in all recovery group animals and normal in all juvenile animals, **indicating that E1$^{v1.11}$ has no effect on these parameters** (**Figure 5**).

Tissue Histopathology Findings:

No gross abnormalities were noted during necropsy in any animals at any time point. Histopathologic analysis was performed at IDEXX Bioanalytics by a boarded anatomic pathologist. All histopathologic findings (background and procedure-related lesions) from the "Adult Repeat Dose Intrathecal" animals are represented in **Figure 6**. Results from the Juvenile study were similar. In the final pathologist report, the following summary was provided: **Spurious, incidental and background findings (not treatment-related) were noted in the kidneys and liver across all treatment groups including controls.** Minimal subarachnoid inflammation in spinal cord sections was limited to the high dose group. Minimal to mild mononuclear inflammatory infiltrates were observed in leptomeninges of fore- and mid-brain sections in the vehicle control (PBS only), 3.5 mg and 9.0 mg dosing groups, with increased frequency in control-injected and 9.0 mg groups in the adult intrathecal study. The data indicate that a dose-related effect is not present for this finding. **Consistent with this, all underlying neuropil and parenchyma in the brain and spinal cord and all available dorsal root ganglia appeared normal with no lesions.** Representative tissue images of kidney, liver and dorsal root ganglia sections from Adult Repeat Dose Intrathecal animals show no signs of pathology (**Figure 7**).

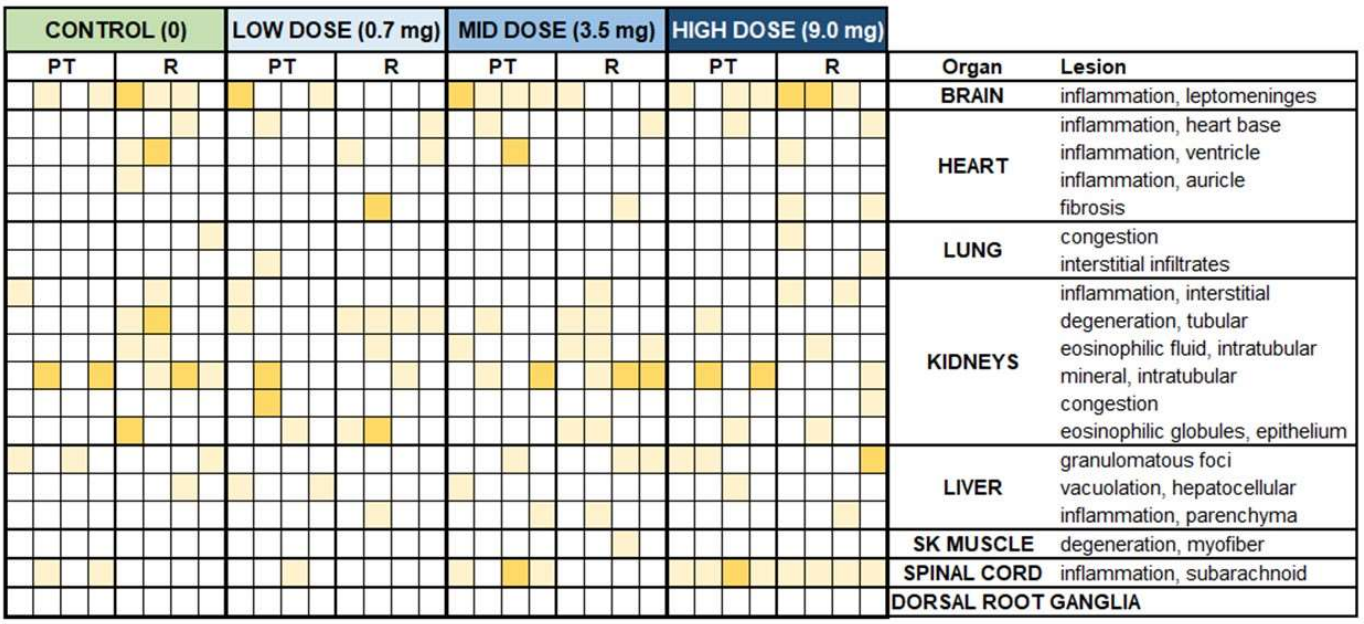


Figure 6: **Histopathologic scoring of Adult Repeat Dose Intrathecal Injection SD Rats by boarded anatomic pathologist from IDEXX Bioanalytics.** Scores are reported at 0-4, half points were rounded up. Each box represents a tissue and possible finding from each animal in the Post-Treatment (PT) and Recovery (R) groups. No scores were > 2 for any tissue in the study.

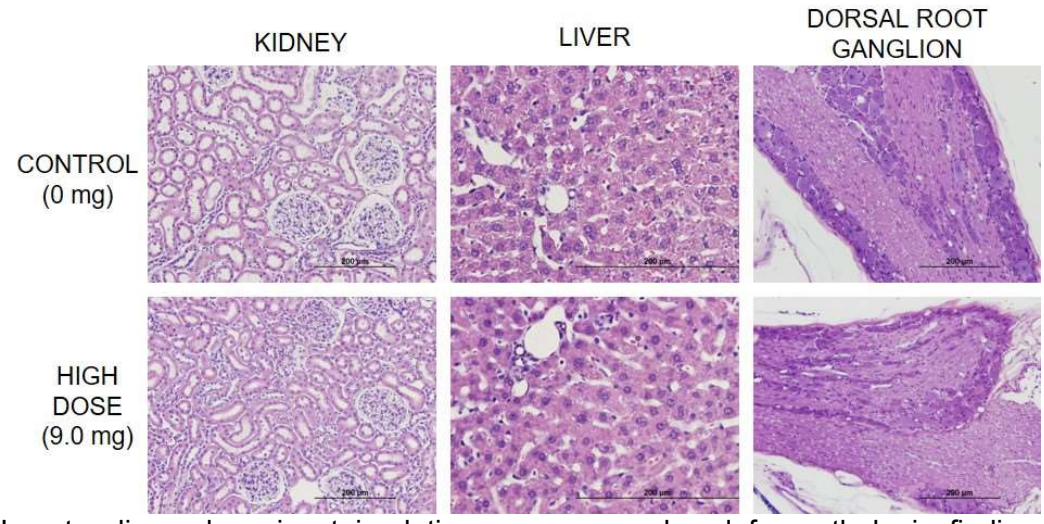


Figure 7: Hematoxylin and eosin stained tissues were analyzed for pathologic findings by IDEXX Bioanalytics on all animals. Kidney, liver and dorsal root ganglion were unaffected by drug and representative samples are shown here from control (0 mg) and high dose (9.0 mg).

$E1^{v1.11}$ Pharmacokinetics Studies in progress

Juvenile CD-1 mice were used to assess short-term pharmacokinetics of $E1^{v1.11}$ following a single, ICV injection of 0, 27, 134, 670 μg of $E1^{v1.11}$ within 36 hours of birth. Plasma and tissue (brain, liver, kidney, etc.) samples were be collected at 5 min - 72 hrs and assessed for $E1^{v1.11}$ levels using an custom ELISA assay. Results demonstrated a dose-response dependency (**Figure 3**) for the brain. $E1^{v1.11}$ levels were present in the brain, increasing quickly and decreased over 24-72 hrs. $E1^{v1.11}$ levels in the kidneys increased later than the brain, as expected, and began decreasing by 12 hrs post-injection. The levels in the liver showed a similar pattern as the kidneys at a much lower absorption level. These kinetic trends are similar to other ASOs that have been studied. The current analysis plots semi-quantitative data that has not been normalized to total animal body concentrations relative to injection amounts. This analysis is on-going. Additionally, longerterm PK experiments are under-way (with $E1^{v1.11}$ levels being monitored for over 90 days from injection.

To assess longer-term pharmacokinetics, 10-week old SD rats received a single, intrathecal dose of 0, 20, 100, and 250 μg of $E1^{v1.11}$. Plasma and tissue samples (brain, spinal cord, kidney, and liver) were taken at 4 hr, and 30, 60, and 90 days post-dose (no acute deaths were observed in this study as well). The later time points are ongoing and will be completed in March 2020. Sample analysis will be completed upon final sacrifice.

Further analysis of these samples is under way, using LC-MS in addition to Elisa analysis. Both methods will be analyzed for sensitivity, specificity and reproducibility in order to drive the choice of assay to be used in future GLP studies. This analysis will be complete by May of this year. Preliminary assay validation data on spiked samples suggest that both methods will be viable.

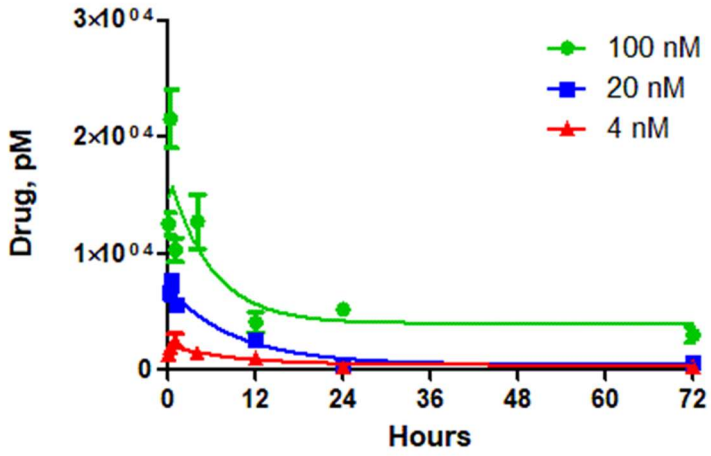


Figure 8: **Preliminary short-term PK of $E1^{v1.11}$.** Data has not been normalized to tissue size and animal size versus injection volume. Level in the liver showed similar kinetics as the kidneys at much lower levels with a delayed peak concentration (unpublished data).

Aim 4: Detection and analysis of the E1$^{v1.11}$ PMO for purity and stability studies.

The main focus during this period on task 4 was the synthesis, analysis, formulation, etc. for the materials to be used in our GLP studies, in order to perform the appropriate stability measurements on both the drug substance and drug product.

1.1 Drug Substance

E1$^{v1.11}$ is synthesize using a solid phase synthesis approach where a solid support is activated, followed by subsequent additions of each base pair of the sequence, with

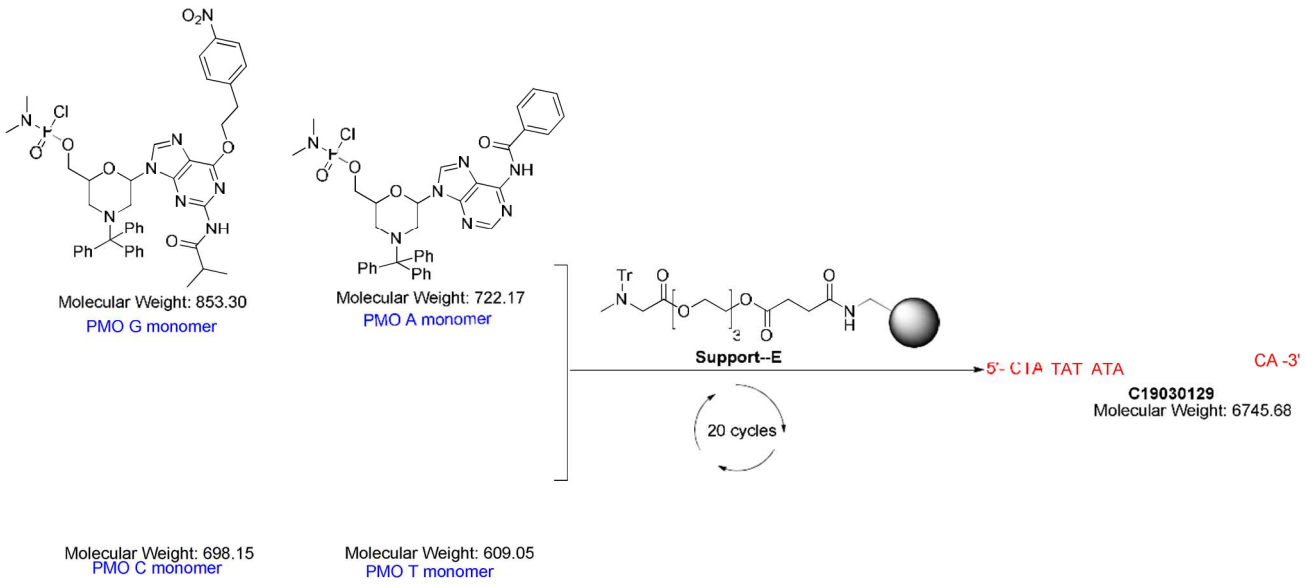
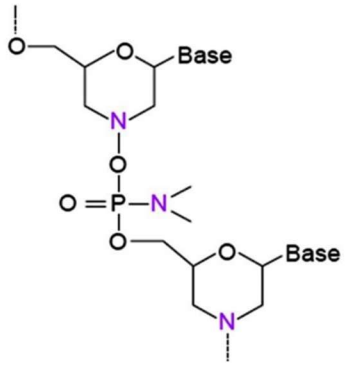


Figure 9: Synthesis Scheme of E1$^{v1.11}$ used to produce the research grade materials used for our previous studies.

various protection, deprotection, washing steps, etc., in between (**Figure 9**). Thus, the manufacturing process itself has internal purification steps after each base pair addition, making the final product relatively pure once it is cleaved from the product and collected. Once synthesized and cleaved from the column, the material undergoes AEX chromatography purification, followed by de-salting and lyophilization. Synthesis and purification will follow the already validated methods by STA provided to the FDA in our pre-IND meeting material.

The structure of $E1^{v1.11}$ is shown in Figure 10. Replacement of anionic phosphates of DNA with the uncharged phosphorodiamidate groups of a Morpholino eliminates ionization in the usual physiological pH range, so Morpholinos in organisms, cells, or in water are uncharged. Morpholino oligos are much more stable than DNA and are not sensitive to nucleases.



Sequence of $E1^{v1.11}$:

5'- CTATATATAGTTATTCAACA -3'

Figure 10: $E1^{v1.11}$ backbone structure and sequence.

These materials we analyzed under GMP conditions and the data was presented to the FDA as part of our pre-IND meeting (Figure 11). A synopsis of the data is shown below.

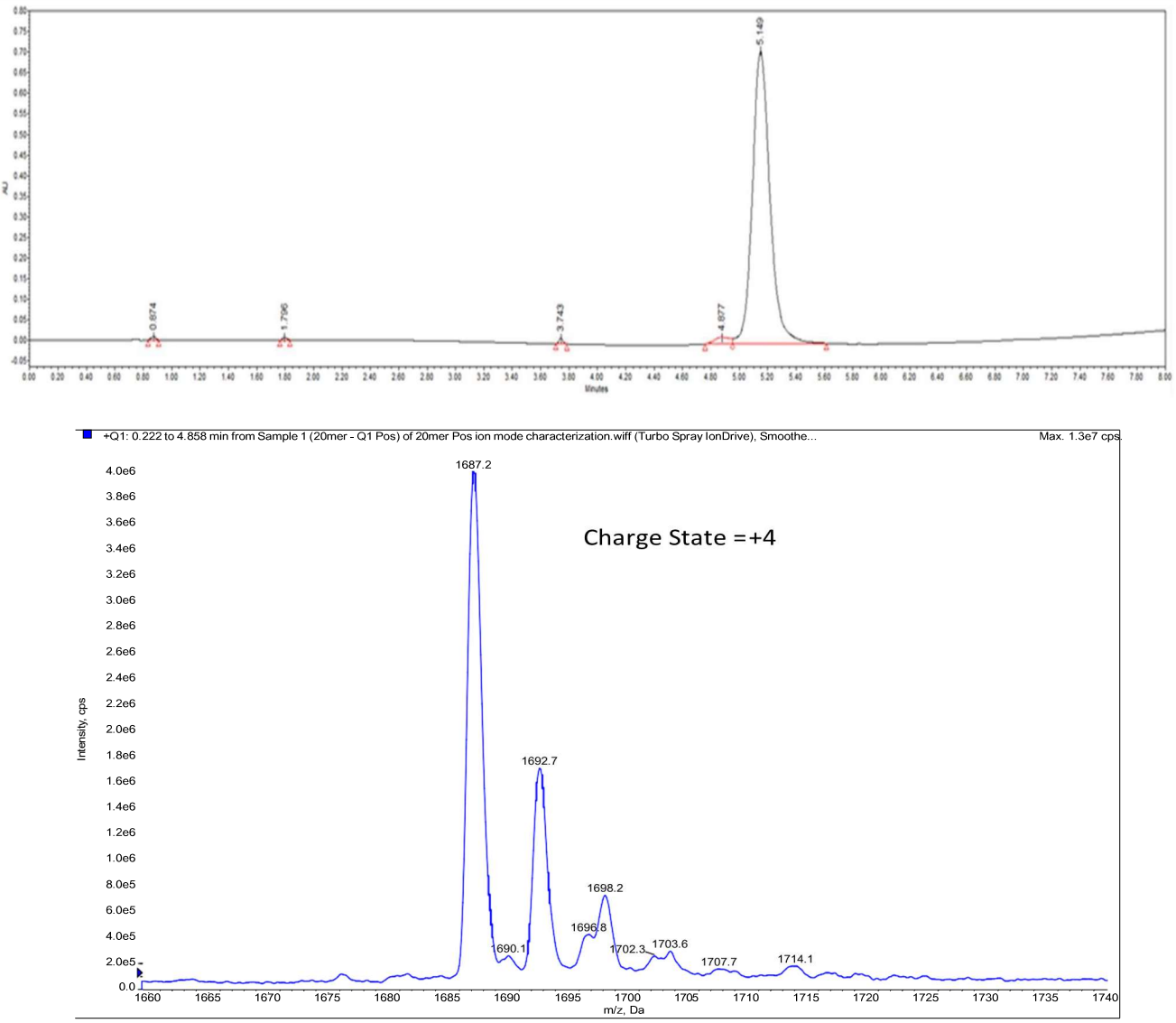


Figure 11: (TOP) HPLC-UV Chromatogram of E1$^{v1.11}$ HPLC Chromatogram of E1$^{v1.11}$ after purification (Abs: 260 nm) of research grade material. (**BOTTOM**): Mass Spectra around 1700 amu. of E1$^{v1.11}$. The peaks at 1692.7, 1698.2, etc. represent the E1$^{v1.11}$ with additional [Na] ions (unpublished data).

Aim 5: IND application

A large amount of work was performed during this period analyzying data and preparing our pre-IND meeting package for the FDA. Feedback was received from the FDA on our proposed experiment protocols for GLP animal studies and CMC plan.

Timeline:

Pre-IND package submitted	October 2019
Initial written FDA feedback	November 2019
Shift follow on questions to FDA	January 2020
FDA final comments/confirmations received	February 2020

For brevity, we will not describe all of the proposed studies in this document. The final feedback from the FDA was positive feedback on all of our proposed studies and CMC proposed specification and analytical techniques.

The FDA has approved the study designs both for our GLP animal studies and CMC program. They have agreed with the number and type of animals to be used, the assays to be performed, experimental design, etc. The protocols reviewed were prepared by Shift in collaboration with Charles River Labs. The specific aims and experimental designs in Shift's Create Bio grant application 1 outline exactly what was presented to the FDA and approved as viable to initiate Phase 1 clinical trials (assuming the adequacy of data from the experiments is reviewed and acceptable).

Concurrent with clinical development (but not required to initial trials), the FDA is recommending:

- 6-month subcutaneous study in rat
- Long-term (52-week) study in NHPs that includes expanded neurohistopathology evaluation and learning assessment
- Assessment of the carcinogenic potential of E1$^{v1.11}$ may be submitted post-approval, if the available nonclinical and clinical data support such a strategy

Quotes from the FDA written feedback:

- "The nonclinical studies planned for the initial IND submission would be sufficient to support initiation of clinical studies."
- "The proposed drug substance specifications seem reasonable for a U.S. Phase 1."

As part of Aim 5, Shift has been working closely with the FDA. Three pre-pre-IND meetings (electronic communication) occurred between Shift and the FDA. All of the proposed experiments were reviewed and considered "acceptable" by the FDA.

Shift received notification of Orphan Drug Status on March 4, 2020 (DRU-2019-7270) for E1$^{v1.11}$.

Shift has recruited and hired a Chief Medical Officer to begin working closely with the FDA. Dr. Todd Lorenz joined Shift in October, 2020.

Shift has successfully recruited the head of our Medical Advisory Panel, Dr. John Day. Dr. Day is a leader in clinical trial research in the neuromuscular space and is the Director, Neuromuscular Division and Clinics at Stanford University. Dr. Day ran SMA clinical trials for Spinraza and Zolgensma as well as ASO-based trials for SRP-4045 and SRP-4053 (DMD). Shift is actively recruiting 3-4 additional key opinion leaders in this space with Dr. Day's assistance.

Studies to be completed prior to final IND approval:

13-Week Intrathecal Toxicity Study in Monkeys with an 8-Week Recovery Period (GLP)
The objective of this study is to determine the potential toxicity of E1$^{v1.11}$ for the treatment of spinal muscular atrophy, when given intrathecally, bi-weekly for 13 weeks to non-human primates and to evaluate the potential reversibility of any findings. In addition, the toxicokinetic characteristics of E1$^{v1.11}$ will be determined.

13-Week Toxicity Study in Juvenile Rats with an 8-Week Recovery Period (GLP)
The objectives of this study are to determine the potential toxicity of E1$^{v1.11}$ when given subcutaneously for 13 weeks to juvenile rats and to evaluate the potential reversibility of any findings. In addition, the toxicokinetic characteristics of E1$^{v1.11}$ will be determined.

Intrathecal Dose-Range Finding Study in Monkey (non-GLP)
The objective of this study is to determine the potential dose-range-finding toxicity of E1$^{v1.11}$ for the treatment of spinal muscular atrophy, when given as a single intrathecal dose to non-human primates. In addition, the toxicokinetic characteristics of E1$^{v1.11}$ will be determined.

What were the major goals of the project?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project identify these dates and show actual completion dates or the percentage of completion.

The overarching goal of this project is to provide critical pre-clinical data as we move our lead compound, E1v1.11, to an IND submission with the FDA.
Aim 1: Dose-escalation in SMA mice
Aim 2: SMN protein levels in SMN2 mice
Aim 3: PK/toxicity studies
Aim 4: Examine compound stability
Aim 5: IND application

What was accomplished under these goals?
For this semi-annual reporting period only describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided.

During the third reporting period (April 1, 2020-October 30, 2020), the team continued to meet virtually at least twice weekly, with smaller breakout groups meeting more frequently. Due to Covid-restrictions placed on many institutions, including research and infrastructure at the University of Missouri, research on campus slowed although progress continued on this project through our vendor collaborations. A summary of all completed work is as follows:
Aim 1: Completed
Aim 2: In progress
Aim 3: PK/toxicity studies **completed**
Aim 4: No new results to report
Aim 5: Three pre-pre-IND meetings (electronic communication) occurred between Shift and the FDA. All of the proposed experiments were reviewed and considered “acceptable” by the FDA.

Describe the Regulatory Protocol and Activity Status (if applicable).

Describe the Protocol and Activity Status for sections a-c, as applicable, using the format described for each section. If there is nothing significant to report during this reporting period, state “Nothing to Report.”

(a) *Human Use Regulatory Protocols*

No human subject research is part of this grant.

(b) Education or Training

“Cadaver” is defined as a deceased person or portion thereof, and is synonymous with the terms “human cadaver” and “post-mortem human subject” or “PMHS.” The term includes organs, tissues, eyes, bones, arteries or other specimens obtained from an individual upon or after death. The term “cadaver” does not include portions of an individual person, such as organs, tissue or blood, that were removed while the individual was alive (for example, if a living person donated tissue for use in future research protocols, that tissue is not considered a “cadaver” under this policy, regardless of whether the donor is living or deceased at the time of tissue use).

***TOTAL ACTIVITIES**: State the total number of RDT&E, education or training activities that will involve cadavers. If not applicable, write “No RDT&E, education or training activities involving human cadavers will be performed to complete the Statement of Work (SOW).”*

TOTAL ACTIVITIES: No RDT&E, education or training activities involving human cadavers will be performed to complete the Statement of Work (SOW)."

ACTIVITES:

(c) Animal Use Regulatory Protocols

TOTAL PROTOCOL(S):

State the total number of animal use protocols required to complete this project (e.g., 2 animal use research protocols will be required to complete the Statement of Work.). If not applicable, write "No animal use research will be performed to complete the Statement of Work."

PROTOCOL(S):

List the identifier and title for all animal use protocols needed to complete the project. Include information about the approved target number for statistical significance, type of submission, type of approval with associated dates, and performance status.

The following format shall be used:

Protocol (of total):

Protocol [ACURO Assigned Number]:

Title:

Target required for statistical significance:

Target approved for statistical significance:

Submitted to and Approved by:

Provide bullet point list of protocol development, submission, amendments, and approvals (include IACUC in addition to ACURO).

Status:

Provide bullet point list of performance and/or progress status relating to the above protocol and discuss any administrative, technical, or logistical issues that may impact performance or progress of the study (e.g. animal use protocol needs revision to minimize animal suffering, animal protocol modification to include additional staff) for the above ACURO approved protocol.

TOTAL PROTOCOL(S): 2

PROTOCOL 1 of 2 total: 1

Protocol [ACURO Assigned Number]: PR171107.e001

Title: Therapeutic analysis in animal models of neurodegeneration Target required for statistical significance:

Aim 1;

E1$^{v1.11}$ treated:	80 SMA mice
"Scrambled" ASO treated:	20 SMA mice
Vehicle treated:	20 SMA mice
Untreated:	20 SMA mice
Total:	140 SMA mice

Aim 2;

E1$^{v1.11}$ treated:	80 *SMN2* transgenic mice (20 per group)
"Scrambled" ASO treated:	20 *SMN2* transgenic mice
Vehicle treated:	20 *SMN2* transgenic mice
Untreated:	20 *SMN2* transgenic mice
Total:	140 *SMN2* transgenic mice

Aim 3:

E1$^{v1.11}$ 4 mM:	15 mice P10; 15 mice P30; 10 mice P50; 10 mice P100 (50 mice)
E1$^{v1.11}$ 50 mM:	15 mice P10; 15 mice P30; 10 mice P50; 10 mice P100 (50 mice)
E1$^{v1.11}$ 100 mM:	15 mice P10; 15 mice P30; 10 mice P50; 10 mice P100 (50 mice)
E1$^{v1.11}$ 500 mM:	15 mice P10; 15 mice P30; 10 mice P50; 10 mice P100 (50 mice)

PROTOCOL (2 of 2 total): 2

Protocol [ACURO Assigned Number]: **PR171107.e001**

Title: **Therapeutic analysis in animal models of neurodegeneration**

Target required for statistical significance:

E1v1.11 treated: 80 SMN2 transgenic mice (20 per group)

"Scrambled" ASO treated: 20 SMN2 transgenic mice

Vehicle treated: 20 SMN2 transgenic mice

Untreated: 20 SMN2 transgenic mice

Total: 140 SMN2 transgenic mice

Target approved for statistical significance: **Approved as requested**

SUBMITTED TO AND APPROVED BY:

University of Missouri Animal Care and Use Committee as number 9924 (previous approval number 9091) on 7/14/2020. Attending veterinarian Erin O'Connor, IACUC Chair Jeffrey Henegar.

Approved by Animal Care and Use Review Office (ACURO), Department of the Army, Dawn Fitzhugh on 9/22/2020.

STATUS:

Approved and in progress.

What do you plan to do during the next reporting period to accomplish the goals and objectives?

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

Complete and analyze Aim 2 data. Further refinedment and various experiments under aims 3 and 5.

2. Products:

List any products resulting from the project during the reporting period. If there are no products to report for the current quarter, state "Nothing to report."

Examples of products include:

- *publications, conference papers, and presentations;*
- *website(s) or other Internet site(s);*
- *technologies or techniques;*
- *inventions, patent applications, and/or licenses; and*
- *other products, such as data or databases, biospecimen collections, germplasm, audio or video products, software, models, educational aids or curricula, instruments or equipment, data and research material, clinical or educational interventions, or new business creation.*

Nothing to report.

3. Participants & Other Collaborating Organizations

What individuals have worked on the project?

Provide the following information for: (1) Project Directors (PDs)/ PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort).

Provide the name and identify the role the person played in the project. Indicate the nearest whole person month (Calendar, Academic, Summer) that the individual worked on the project. Show the most senior role in which the person worked on the project for any significant length of time. For example, if an undergraduate student graduated, entered graduate school, and continued to work on the project, show that person as a graduate student, preferably explaining the change in involvement.

Describe how this person contributed to the project. If information is unchanged from a previous submission, provide the name only and indicate "no change."

Name: Christian Lorson
Project Role: PI (Shift Pharma)
Researcher Identifier: 0000-0002-1023-2169
Nearest person month worked: 3.0
Contribution to Project: Dr. Lorson is the PI at Shift Pharma. He is responsible for coordinating between Shift and MU and overseeing the overall project design and implementation.

Name: Steve O'Connor
Project Role: (Shift Pharma): CEO **Researcher Identifier:** 0000-0002-9915-5787
Nearest person month worked: 5.1
Contribution to Project: Dr. O'Connor to manage the day-to-day research of the project. He is also responsible for chemistry, manufacturing, and controls program, including analytical methods development, data analysis, particularly for the LC/MS work for the PK analysis, product manufacturing, stability studies, as well as work with our sub-contractors and suppliers. He assisted with all data analysis.

Name: Sarah Hansen
Project Role: (Shift Pharma): Director of Translational Research
Nearest person month worked: 6.22
Contribution to Project: Dr. Hansen managed the day-to-day research of the project. She coordinated and performed much of the animal research presented in this report. She also was responsible for all data acquisition, analysis, and report writing.

Name: Diane Beatty
Project Role: (Shift Pharma): VP of Reg. Affairs and Product Development
Researcher Identifier: 0000-0001-9071-6384
Nearest person month worked: 2.75

Pr

Name: Mona Kacher (replaced Madeline Simon on the project)
Project Role: (MU)
Researcher Identifier: 0000_0003_1744_6933
Nearest person month worked: 12.0
Contribution to Project: Research technician in charge of animal duties and routine colony tasks, and assists with tissue collection.

Name: Monique Lorson
Project Role: (MU):
technical support
Researcher Identifier:
0000-0002-1772-0712
Nearest person month worked: 4.0
Contribution to Project: Coordinating animal duties, ordering, maintaining colony, organizing cages and breeding, as well as assisting with tissue collection.

Name: Kerry "David" Farris (replaced Erkan Osman on the project)
Project Role: (MU): PI of
the subaward **Researcher Identifier:** 0000-0001-7270-
5876 **Nearest person month worked:** 1.0
Contribution to Project: Dr. Farris coordinated with Shift regarding animal studies and has overseen the personnel at MU.

Name: Madeline Simon (Update per departure—WHEN DID SHE LEAVE?)
Project Role: (MU):
technical support
Researcher Identifier:
0000-0002-6936-908X
Nearest person month worked: 3.0
Contribution to Project: Research technician in charge of animal duties and routine colony tasks, and assists with tissue collection.

Name: Toni Morcos (left this project Jan 2020)
Project Role: (MU)
Researcher Identifier: 0000-0002-7729-070X
Nearest person month worked: 1.0
Contribution to Project: Assists in the lab for general lab related activities, assists with colony maintenance, PCR and genotyping.

4. Changes/Problems: The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

a. Actual Problems or delays and actions to resolve them

Research was delayed on Aim 2 during this reporting period due to Covid-19-related university-wide shutdown. Specifically, while colonies could be maintained, no other research was allowed for several months with the except of SARS-CoV-2-directed work. Despite this, at the current time, we are able to obtain access again to the vivaria and laboratory and are able to proceed as planned.

Research was delayed on Aim 3 during this reporting period due to Covid-19 related shutdowns, both at the university and certain suppliers. Toxicity results for this aim were not delayed but certain PK analysis was delayed.

b. Anticipated Problems/Issues

Provide a description of anticipated problems or issues that have a potential to impede performance or progress. Also provide course of actions planned to mitigate problems or to take should the problem materialize.

None to report

5. Special Reporting Requirements:

Quad Charts: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.