Introduction

LNP delivery vehicles are comprised of novel lipid excipients and chronic medicines require repeat dosing via systemic administration, there is a need to assess the cardiovascular (CV) safety of the LNP components.

Cardiovascular assessments are traditionally performed via telemetry implantation or external jacketed monitors. Star-Oddi data loggers are implanted subcutaneously for the collection of heart rate and body temperature.

The benefits of data loggers compared to traditional implanted telemetry models are that the data loggers are less invasive, and still allow for continuous/uninterrupted heart rate and body temperature data collection. Use of data loggers may provide a minimally invasive option for investigation of mRNA-1944-related heart rate and body temperature changes in rats in place of nonhuman primates, supporting 3Rs goals in animal research.

The goals of the study were:

Determine the sensitivity of a subcutaneously implanted device (Star-Oddi) in Sprague Dawley rats when compared with a standard telemetry-implanted device (DSI) within the same animal.

Determine if the rat is a suitable model for assessment of mRNA-1944-related changes.

Methods

Eight rats were dually implanted with a DSI® transmitter (HD-510) and a Star-Oddi DST Micro HRT data logger for the collection of heart rate and body temperature data.

Animal care and use was performed in conformance with the Guide for the Care and Use of Laboratory Animals in an AAALAC-accredited facility.

DSI transmitters were implanted at DSI (St. Paul, MN) and arrived at Labcorp where Star-Oddi data loggers were implanted via a small subcutaneous pocket created in the scapular region. The data logger was secured in the pocket facing the skin with non-absorbable suture utilizing the provided suture eye and a single tack to prevent rotation and excessive movement.

Eight dually (DSI and Star-Oddi) implanted rats were administered the drugs using a double Latin square crossover design in multiple phases (1 & 2) and heart rate (HR) and body temperature (BT) data were collected continuously for 22.5 hours. Implants were removed and data downloaded after Phase 1. Animals were implanted with new Star-Oddi data loggers prior to Phase 2.

Phase 1: Animals were administered amphetamine via SC injection at 0, 0.3, 1 or 3 mg/kg.

Phase 2: Animals were administered mRNA-1944 as administered IV slow bolus at 0.3, 1, 3 mg/kg.

We utilized this specific mRNA because the protein-encoded by mRNA-1944, a chimeric virus (CHIV), monovalent neutralizing antibody, is not pharmacologically active in normal, unreconstituted animals, therefore, results will be attributed to LNP.

Statistical analysis: Data were binned into 5 time periods, and HR and BT were analyzed for each time period using analysis of variance (ANOVA), investigating differences due to treatment. Fitted period means for each dose level were calculated using the parameter estimates from the ANOVA model. Comparisons with vehicle control were made using the fitted means. Confidence intervals (CI) for these treatment comparisons were also calculated (Figure 2). A zero is not included within the 95% confidence interval. This indicates statistical significance at the 5% level (i.e., P ≤ 0.05).

The smallest statistically detectable difference (SSDD) was calculated as the smallest Fisher’s least significant difference at the 5% level (i.e., P ≤ 0.05).

The smallest statistically detectable difference (SSDD) was calculated as the smallest Fisher’s least significant difference (SSD), i.e., width of the 95% confidence intervals) and the median value was reported.

Results

Phase 1

An amphetamine-related increase in heart rate was detected by DSI and Star-Oddi devices and peak changes were noted 0.5 to 3 hours postdose. Both devices had similar median sensitivity (SSDD values).

Table 1: Comparison of heart rate and body temperature data acquired with both Star-Oddi data loggers and DSI telemetry implants. HR and BT increases following the administration of amphetamine at 0.5 to 3 hours postdose are shown. Differences from vehicle control were determined by ANOVA. Similar changes in HR and BT were detected by both technologies.

Table 2: Comparison of smallest statistically detectable differences (SSDD) for heart rate and body temperature data acquired with Star-Oddi data loggers and DSI telemetry implants.

![Figure 1](image1.png) A representative individual animal following administration of 5 mg/kg amphetamine. 1-minute correlation plots for HR (Figure 1a) and BT (Figure 1b). Solid line represents the line of unity. There was a strong correlation between HR measured from Star-Oddi and DSI technologies. There was a linear relationship between Star-Oddi and DSI BT measures; the smallest statistically detectable difference (SSDD) was calculated as the smallest Fisher’s least significant difference (SSD), i.e., width of the 95% confidence intervals) and the median value was reported.

![Figure 2](image2.png) HR and BT time course data following IV bolus administration of vehicle or 0.3, 1 or 5 mg/kg mRNA-1944.

![Figure 3](image3.png) Comparison of the effects of mRNA-1944 on heart rate and body temperature data acquired with both Star-Oddi data loggers and DSI telemetry implants. HR and BT differences from vehicle following the administration of 0.3, 1 or 5 mg mRNA-1944 are shown as a function of time postdose. An mRNA-1944-related increase in HR was detected at 0.5-3 hours postdose at all doses using both technologies.

![Figure 4](image4.png) Representative data from a single animal following administration of 5 mg/kg mRNA-1944. 1-minute mean time course data for HR (Figure 4a) and BT (Figure 4b) demonstrate how closely HR data correlate between DSI and Star-Oddi recordings over time. Body temperature data also track closely, with the 1 degree offset consistently evident. 1-minute box and whisker plots for HR (Figure 4c) and BT (Figure 4d) show similar variance across the two technologies. 1-minute correlation plots for HR (Figure 4e) and BT (Figure 4f) reproduce the 1:1 HR correlation and linear BT relationship with 1 degree offset as observed in Phase 1. Solid line represents the line of unity.

Conclusions

HR and BT data generated with Star-Oddi data loggers and DSI telemetry implants were highly correlated.

Sensitivity measures (SSDD values) for detection of changes in HR and BT were similar between Star-Oddi data loggers and DSI telemetry implants.

mRNA-1944-related changes in HR and BT were detected in rats and could be assessed using both technologies.

Star-Oddi devices offer a less invasive option for earlier assessment of mRNA-1944-induced changes in HR and BT in rats in place of nonhuman primates, consistent with 3Rs principles.

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Disclosures

This study was funded by Moderna, Inc. As 65 and 66 are employees of Moderna, Inc. and may own stock/options in the company.