Cardiovascular assessment of lipid nanoparticle-encapsulating mRNA therapeutics in rats using telemetry and Star-Oddi logger devices

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Introduction

- Lipid nanoparticle (LNP)-encapsulating messenger RNA (mRNA)-based therapeutics and vaccines are an established and emerging drug modality for various indications. The global impact of SARS-CoV-2 mRNA vaccines during the coronavirus-19 pandemic demonstrated the value of mRNA-based platforms in preventing viral-induced serious illness, and several mRNA-based therapeutics are under investigation in clinical trials for chronic disease.
- Given that 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 models. 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-S10) 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 in 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 was administered via IV slow bolus at 0, 0.3, 1 or 5 mg/kg. We utilized this specific mRNA because the protein encoded by mRNA-1944, a chikungunya virus (CHIKV)-monoclonal neutralizing antibody, is not pharmacologically active in normal, uninfected animals; therefore, results will be attributed to LNPs.
- **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). If zero is not included within the 95% confidence interval, this indicates statistical significance at the 5% level (i.e., $P \leq 0.05$).
- The smallest statistically detectable difference (SSDD) was calculated as the smallest Fisher's least significant difference (LSD, i.e., half 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 changed were noted 0.5 to 3 hours postdose. Both devices had similar mean sensitivity (SSDD values).

Dose levels	Star-Oddi HR (beats/minute)	DSI HR (beats/minute)	Star-Oddi BT (˚C)	DSI BT (˚C)
0.3 mg/kg	+43[a]	+38	+0.4[a]	+0.4
1 mg/kg	+46[b]	+60	+0.8[b]	+0.9
3 mg/kg	+47[c]	+52	+1.0[d]	+1.1

a Data only reported for 7 rats due to 1 device failure.
b Data only reported for 6 rats due to 2 device failures.
c Data only reported for 4 rats for due to the poor signal to noise ratio in 3 rats and 1 device failure.
d Data only reported for 7 rats due to 1 device failure.

Table 1. Comparison of heart rate and body temperature data acquired with 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.

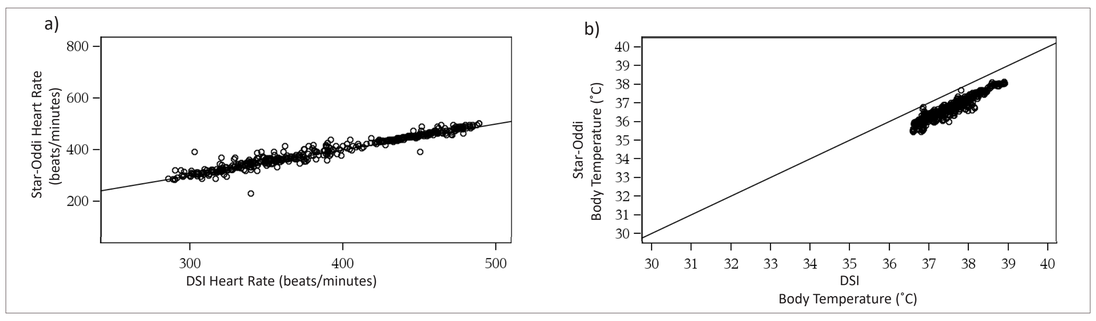

Figure 1. A representative individual animal following administration of 5 mg/kg amphetamine. 1-minute correlation plots for HR (Figure 1a) and BT (Figure 1b). Solid line represents the line of unity. There was a 1:1 correlation between HR measured from Star-Oddi and DSI technologies. There was a linear relationship between Star-Oddi and DSI BT measures; however, Star-Oddi BT measures were consistently ~1˚C lower as would be expected with subcutaneous implantation.

Phase 2

- Dose dependent mRNA-1944-related increases in heart rate and body temperature were detected (Figures 2 and 3).
- A similar magnitude of effect was observed with both the DSI and Star-Oddi devices.
- Sensitivity for detection of HR and body temperature changes was similar in both devices (SSDD values; Table 2).

SSDD (sensitivity)				
	Star-Oddi HR (beats/minute)	DSI HR (beats/minute)	Star-Oddi BT (˚C)	DSI BT (˚C)
Median	20.9	20.8	0.17	0.19

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.

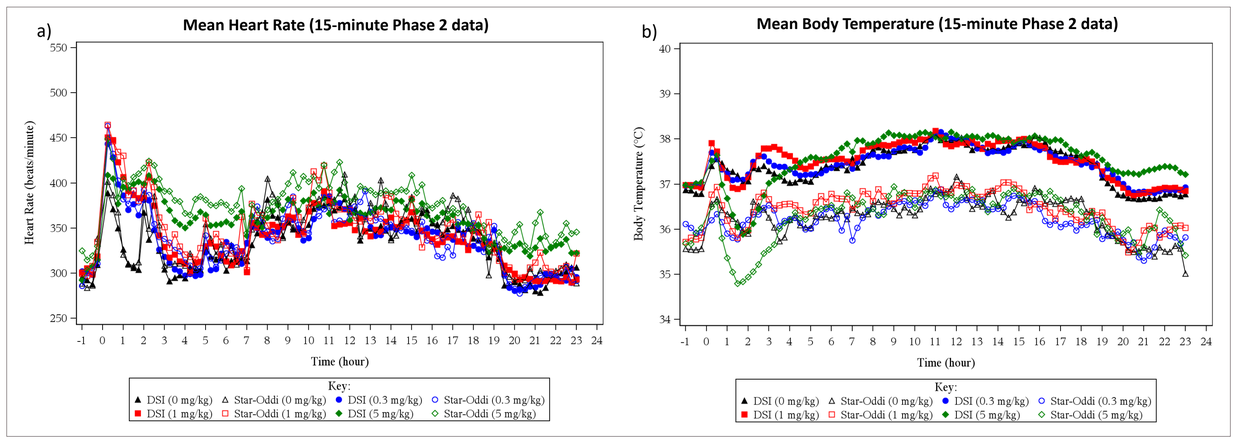

Figure 2. HR and BT time course data following IV bolus administration of vehicle or 0.3, 1 or 5 mg/kg mRNA-1944.

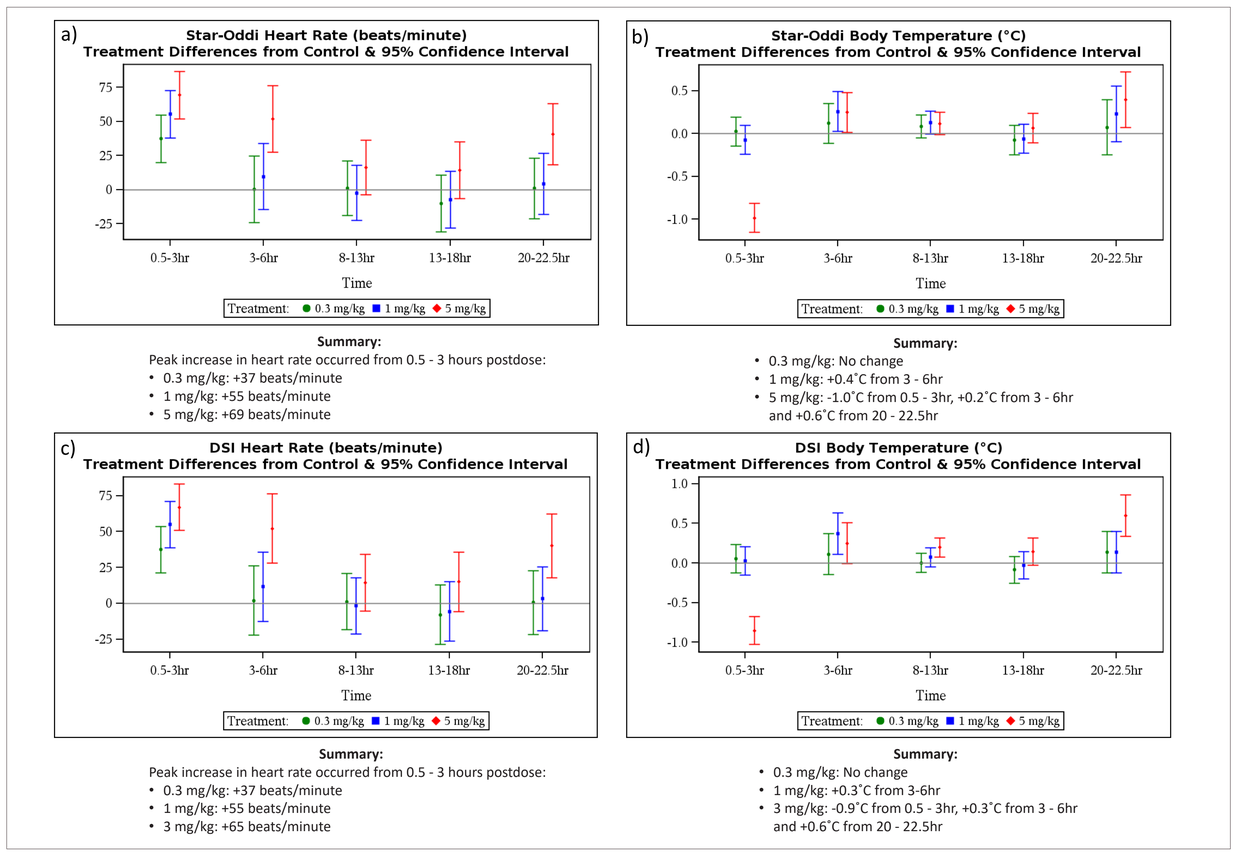

Figure 3. Comparison the effects of mRNA-1944 on heart rate and body temperature data acquired with both Star-Oddi data loggers and DSI telemetry implants. HR and BT differences from vehicle following the administration of 0.3, 1 or 5 mg mRNA 1944 are shown as a function of time period. An mRNA-1944-related increase in HR was detected at 0.5-3 hours post dose at all doses using both technologies. An mRNA-1944-related increase in BT was also detected at 3-6 hours post dose in rats administered 1 mg/kg, while at 5 mg/kg, a biphasic mRNA-1944-related change in BT (decrease from 0.5-3hr followed by an increase from 3-6hr) was observed. Magnitudes of BT changes were similar using both technologies.

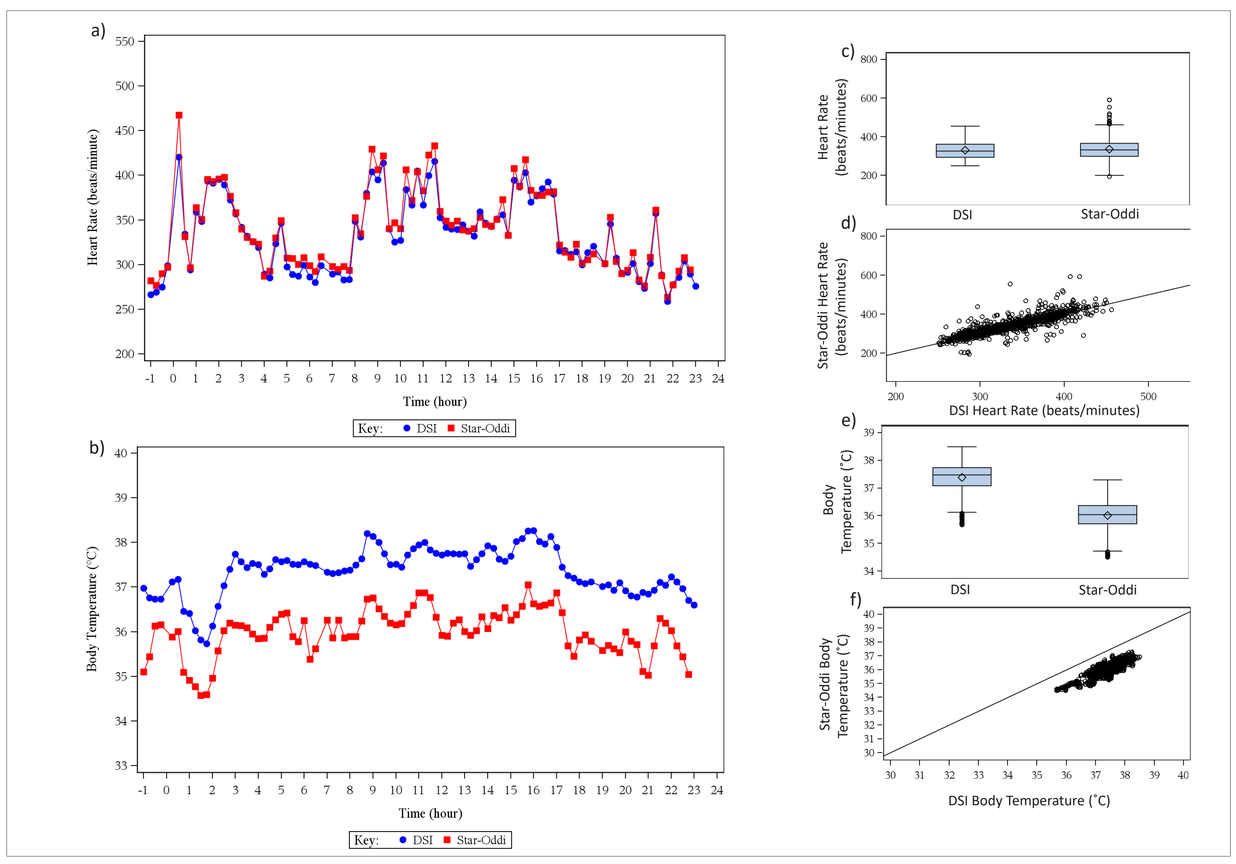

Figure 4. Representative data from a single animal following administration of 5 mg/kg mRNA-1944. 15-minute mean time course data for HR (Figure 4a) and BT (Figure 4b) demonstrate how closely HR data correlate between DSI and Star-Oddi recordings over time. Body temperature data also track closely, with the 1 degree offset consistently evident. 1-minute box and whisker plots for HR (Figure 4c) and BT (Figure 4e) show similar variance across the two technologies. 1-minute correlation plots for HR (Figure 4d) 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.

Disclosures
This study was funded by Moderna, Inc. JW, KG, and SG are employees of Moderna, Inc. and may own stock/stock options in the company.

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