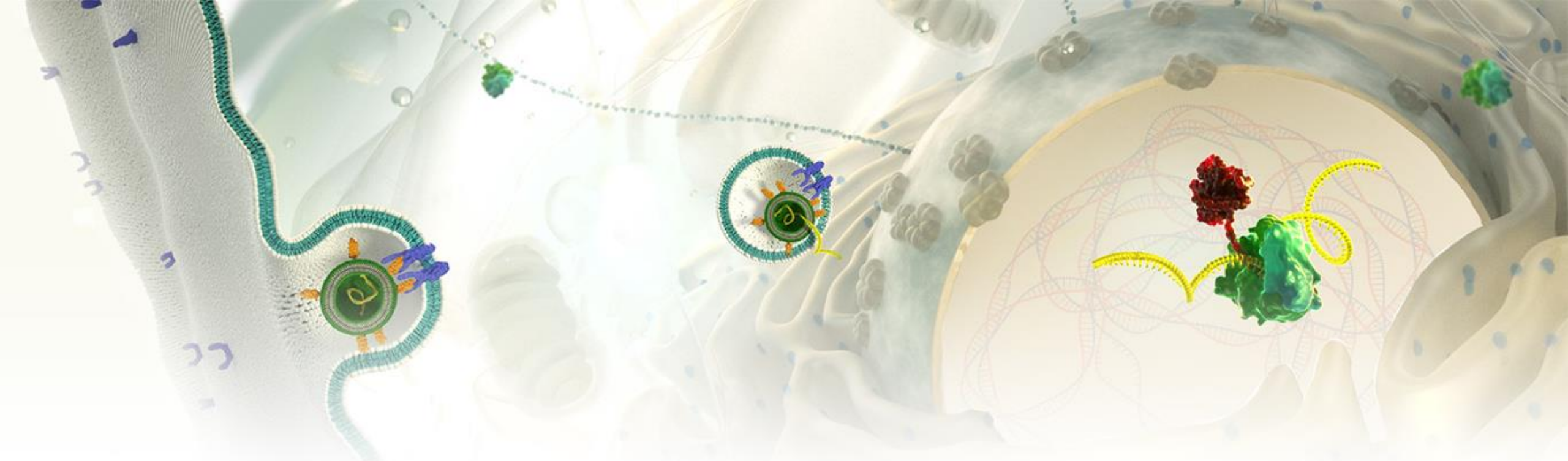

Pharmacodynamic Activity, Pharmacokinetics and Tolerability of Lipid Nanoparticle Formulations of mRNA Following Repeated Intravenous Dosing in Monkeys

Sean Semple

Acuitas Therapeutics

28th Annual Meeting ASGCT, New Orleans, LA

ACUITAS THERAPEUTICS

LNP Technology Clinically Validated

- Acuitas LNP formulation used in ONPATTRO® (Alnylam partnership)
  - First Approved RNAi product (2018)
  - Approved in Canada, US, EU, Japan & elsewhere

- Acuitas LNP formulation used in Comirnaty® (BioNTech/Pfizer partnership)
  - Emergency authorization in Canada, US, EU, UK and elsewhere (2020)
    - First approved mRNA therapeutic (2021)

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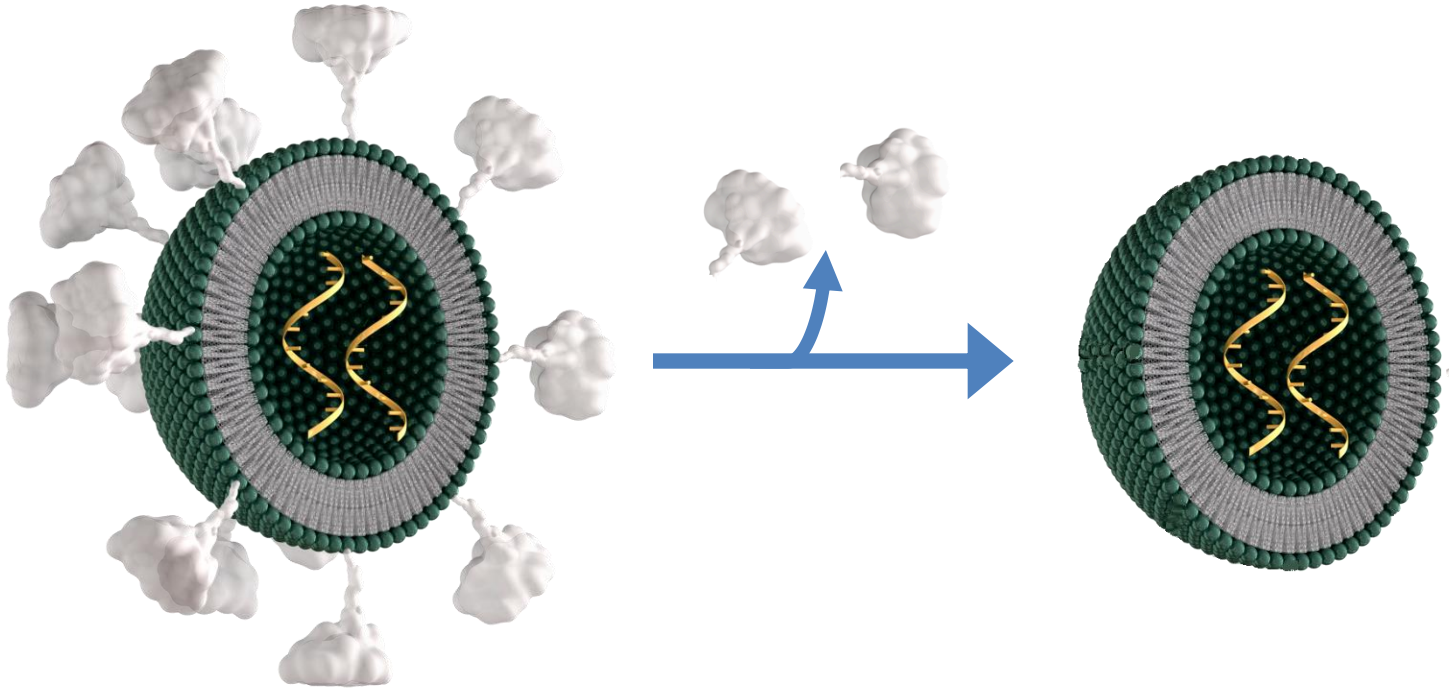
Lipid Nanoparticles (LNP)



Homogeneous, small particles
(<80 nm diameter)

- **Lipids** – integrated components of product
  - **Ionizable lipid** – encapsulation, PK and intracellular delivery
  - **PEG-lipid** – steric barrier; exchanges in vivo
  - **Neutral lipids** – structural lipids
- **Nucleic acid**
  - e.g., mRNA, siRNA, oligonucleotides

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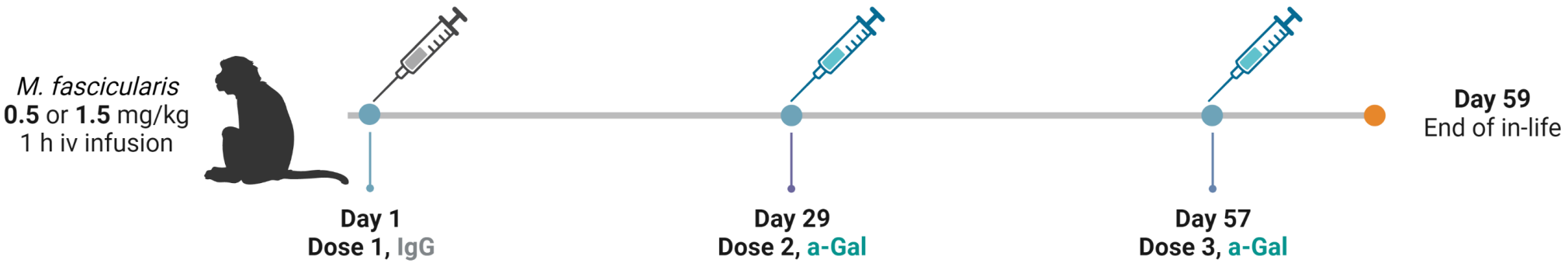
Study Overview



Study Endpoints

PD – Plasma IgG and aGal
PK – iLipid and PEG-lipid
BD – iLipid, PEG-lipid, mRNA
Tox – BW, CP, coag, complement, cytokines, ADA, histopathology

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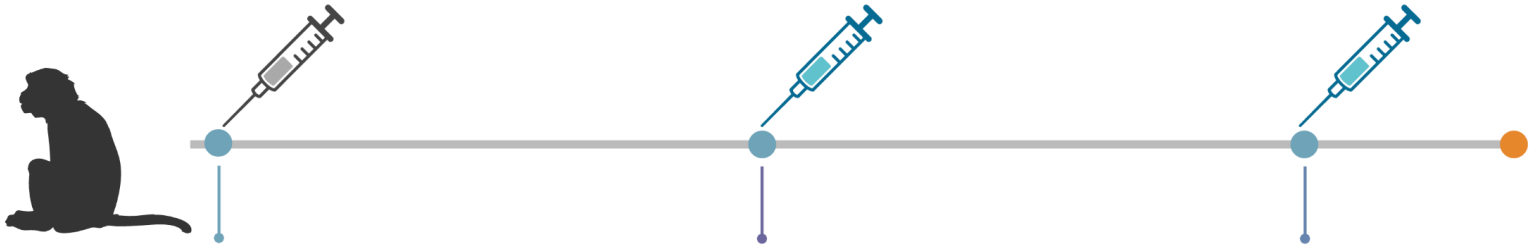
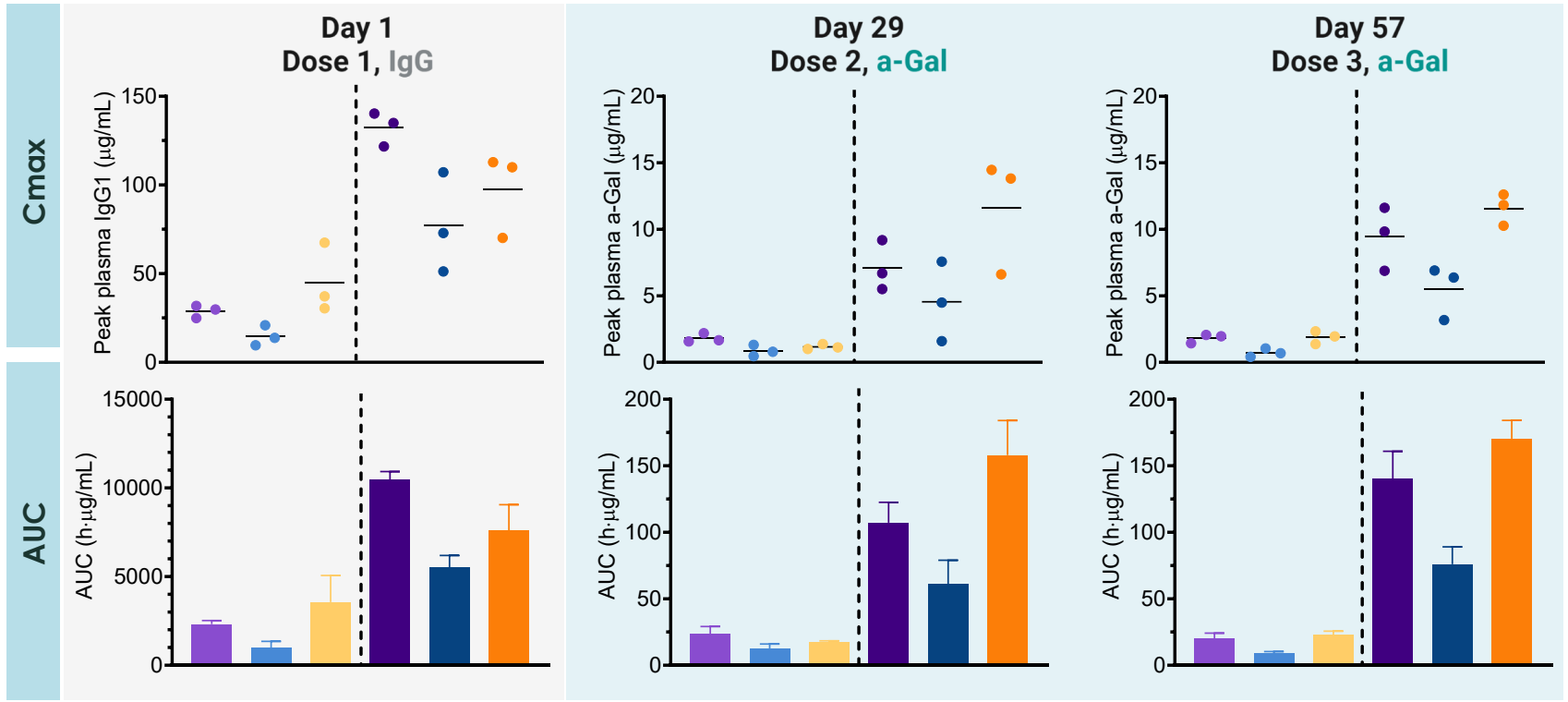
Pharmacodynamics

Consistent Activity Profiles Observed on Repeat Dosing in Monkeys

M. fascicularis
0.5 or **1.5** mg/kg
1 h iv infusion



Day 59
End of in-life



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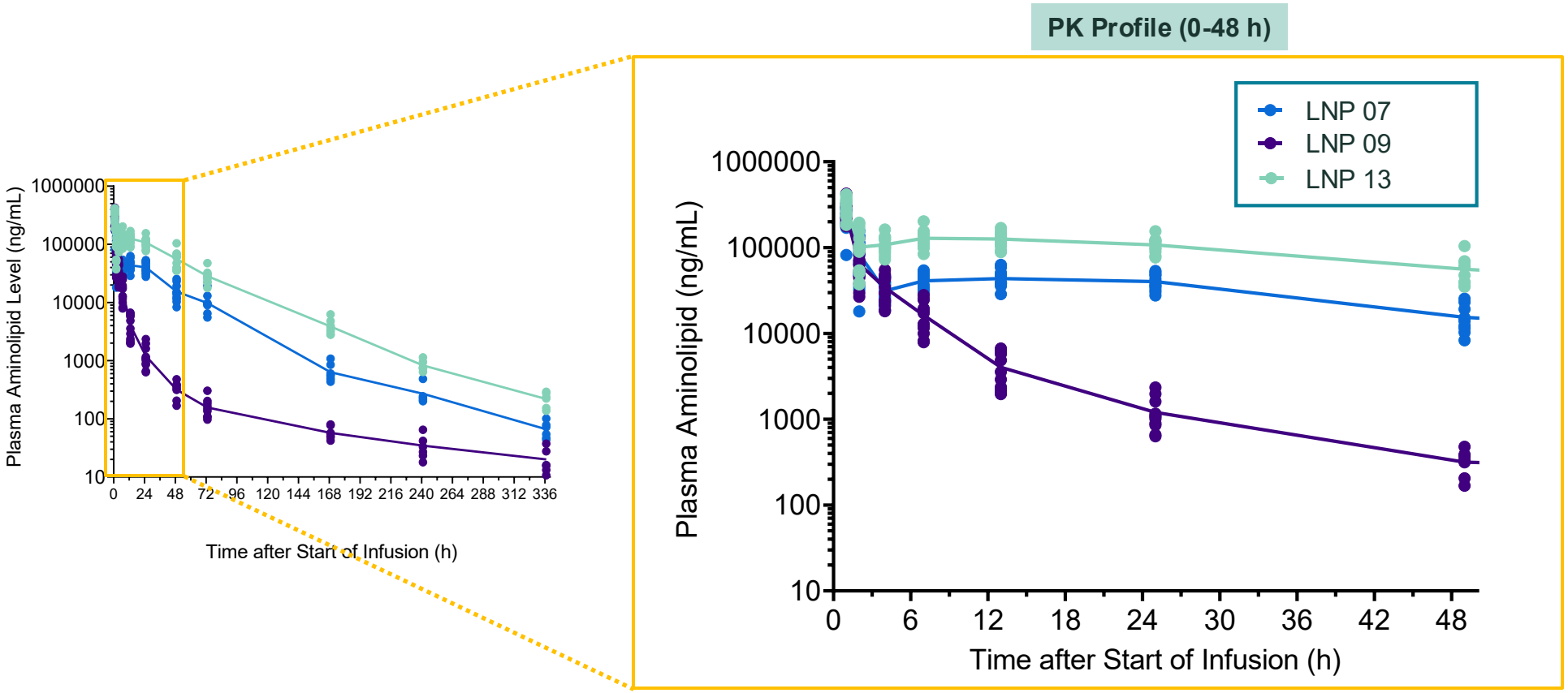
Pharmacokinetics

Different Pharmacokinetic Profiles of LNP and Ionizable Lipid in Monkeys



- Broad range of plasma exposures (~13-fold range of plasma AUC)
- Bi-phasic (LNP 09) and bi-modal ('rebound') profiles (LNP 07 and LNP 13)

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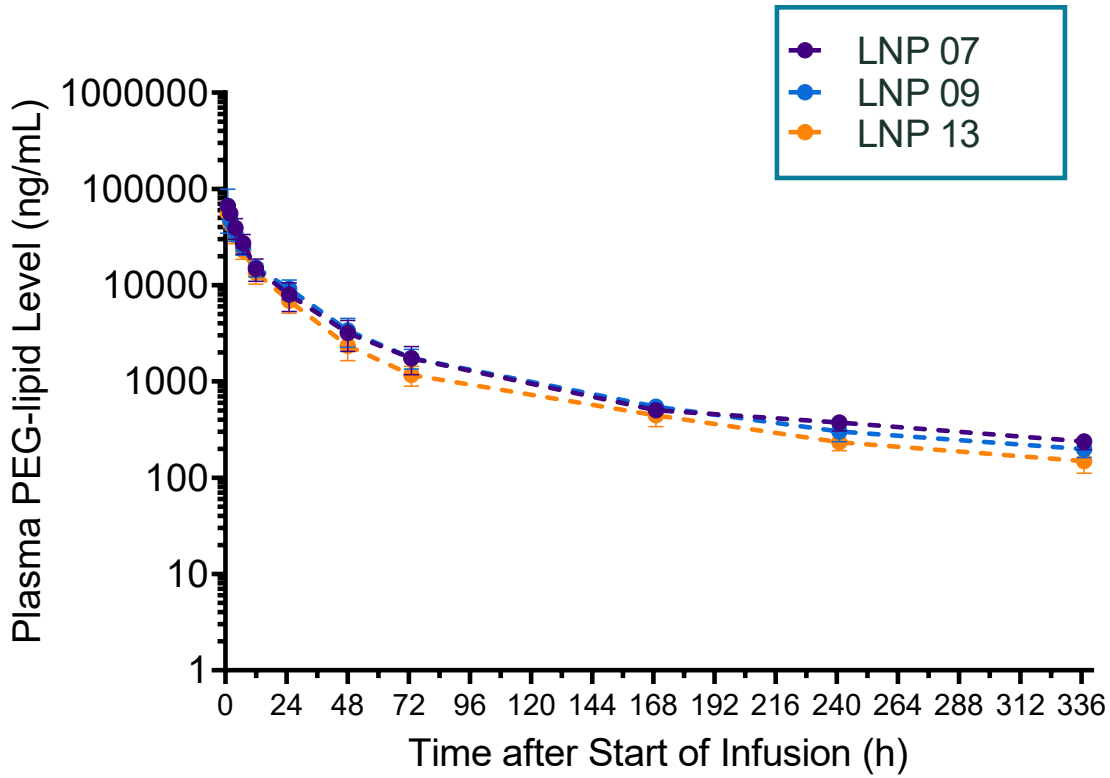
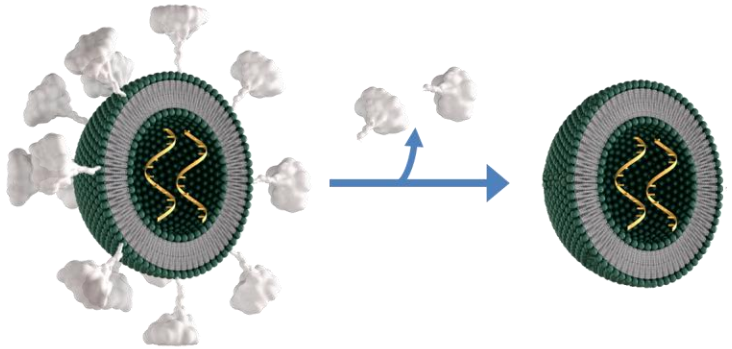
Pharmacokinetics

Plasma PK of PEG-Lipid is Independent of Formulation





- PEG-lipid exchanges out of LNP in the circulation, resulting in overlapping PEG-lipid profiles for all three LNP formulations

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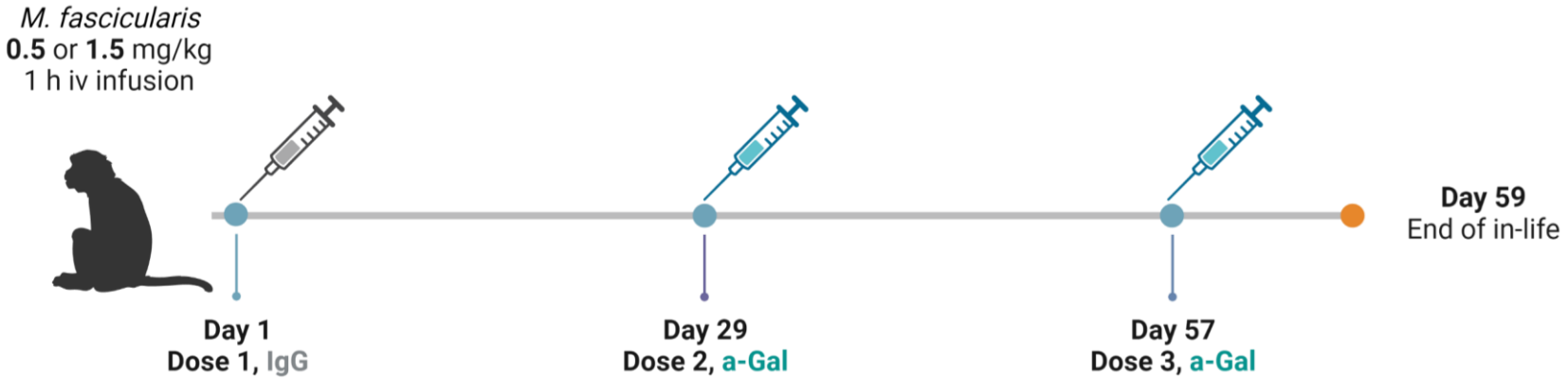
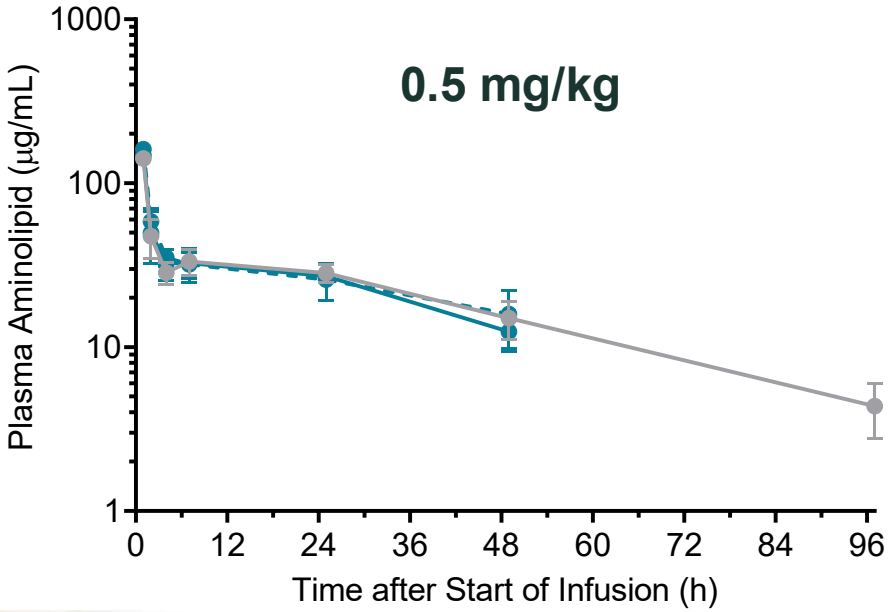
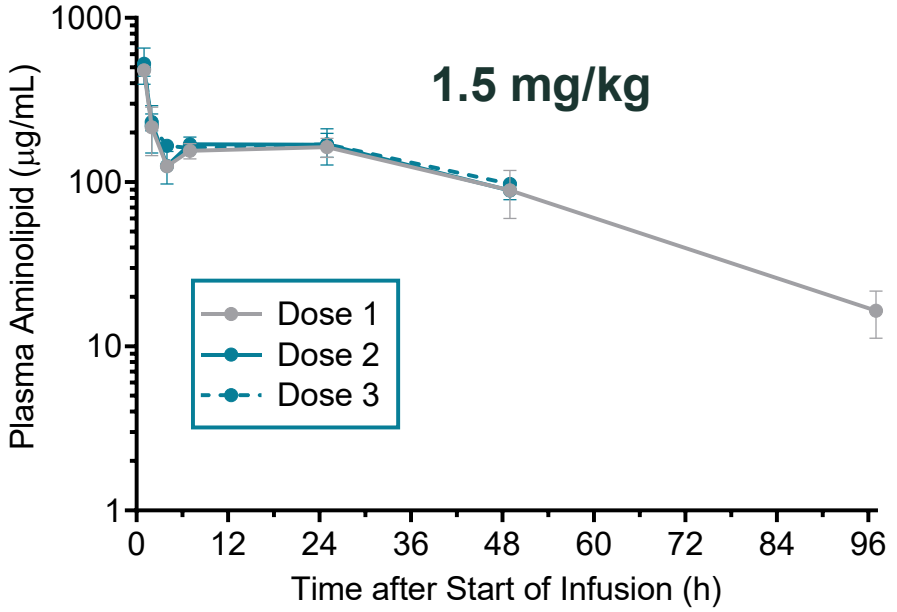
Pharmacokinetics

Plasma PK Profile is Payload-Independent and Consistent Upon Repeated Dosing



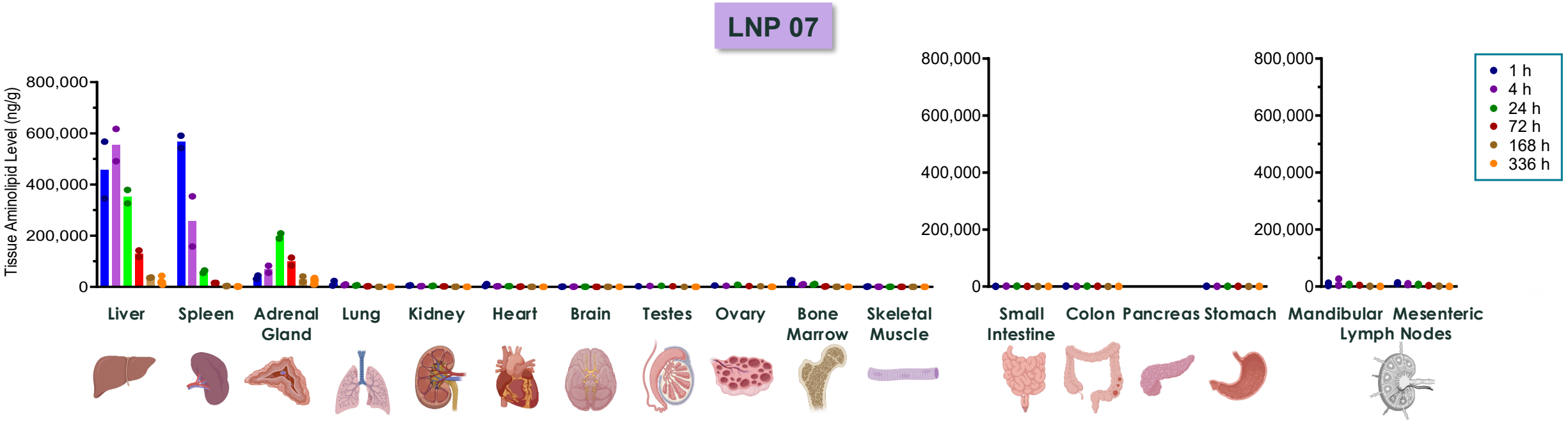
LNP 07





Distribution

Liver, Spleen and Adrenal Glands and No Detection in Germline Cells



- Similar profiles observed for LNP09 and LNP13, except:
  - LNP13: spleen > liver and LNP09: liver > spleen
- No distribution of mRNA into germline cells

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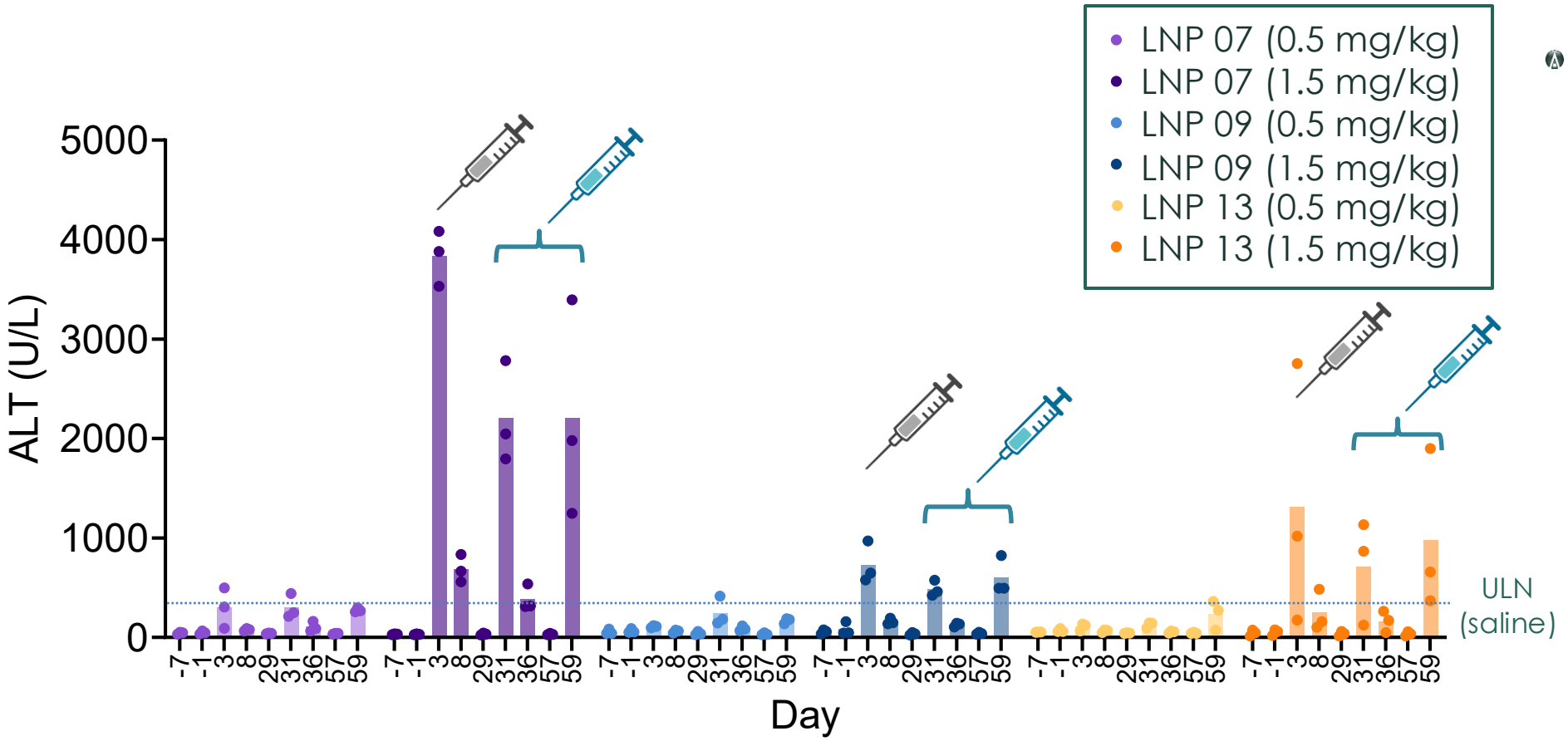
Safety Assessments

Dose-Related, Transient Elevations in Liver Transaminases



- Transient elevations in ALT (and AST)
  - **LNP 07** > **13** > **09**
  - Lower magnitude with αGal payload
  - Magnitude of ALT increase consistent between sequential αGal doses

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Safety Assessments

Findings and Target Organs Typical of LNP – 'Class Effects'

Finding (Day 59, 2 d post-dose)	LNP 07		LNP 09		LNP 13	
	0.5 mpk	1.5 mpk	0.5 mpk	1.5 mpk	0.5 mpk	1.5 mpk
LIVER						
Vacuolation, hepatocyte	2/1/0/0 [4]	0/0/3/0 [9]	3/0/0/0 [3]	2/1/0/0 [4]	2/0/0/0 [2]	0/2/1/0 [7]
Inflammation, mixed leukocyte	0/0/0/0 [0]	0/0/0/0 [0]	3/0/0/0 [3]	3/0/0/0 [3]	1/0/0/0 [1]	2/0/1/0 [5]
Single-cell necrosis, hepatocyte	3/0/0/0 [3]	1/0/2/0 [7]	2/0/0/0 [2]	1/2/0/0 [5]	1/0/0/0 [1]	1/0/1/0 [4]
Swollen, hepatocyte	1/0/0/0 [1]	1/2/0/0 [5]	0/0/0/0 [0]	3/0/0/0 [3]	3/0/0/0 [3]	1/0/2/0 [7]

Grading and Incidence: Minimal/Mild/Moderate/Marked, e.g., 2/1/0/0 = 2 animals graded minimal and 1 animal graded mild; [sum of severity scores]

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Safety Assessments

Findings and Target Organs Typical of LNP – 'Class Effects'

Finding (Day 59, 2 d post-dose)	LNP 07		LNP 09		LNP 13	
	0.5 mpk	1.5 mpk	0.5 mpk	1.5 mpk	0.5 mpk	1.5 mpk
SPLEEN						
Vacuolation, cytoplasm, red pulp	3/0/0/0 [3]	1/2/0/0 [5]	3/0/0/0 [3]	3/0/0/0 [3]	0/1/1/0 [5]	0/2/0/0 [4]
Depletion, lymphoid	0/0/0/0 [0]	0/0/0/0 [0]	0/0/0/0 [0]	0/0/0/0 [0]	0/0/0/0 [0]	0/2/1/0 [7]
Necrosis, red pulp	0/0/0/0 [0]	0/0/0/0 [0]	0/0/0/0 [0]	0/0/0/0 [0]	0/0/0/0 [0]	0/0/2/1 [10]
ADRENAL GLAND						
Depletion, lipid, cortex	0/0/0/0 [0]	0/0/0/0 [0]	0/0/0/0 [0]	0/0/0/0 [0]	0/0/0/1 [4]	1/0/0/2 [9]

Grading and Incidence: Minimal/Mild/Moderate/Marked, e.g., 2/1/0/0 = 2 animals graded minimal and 1 animal graded mild

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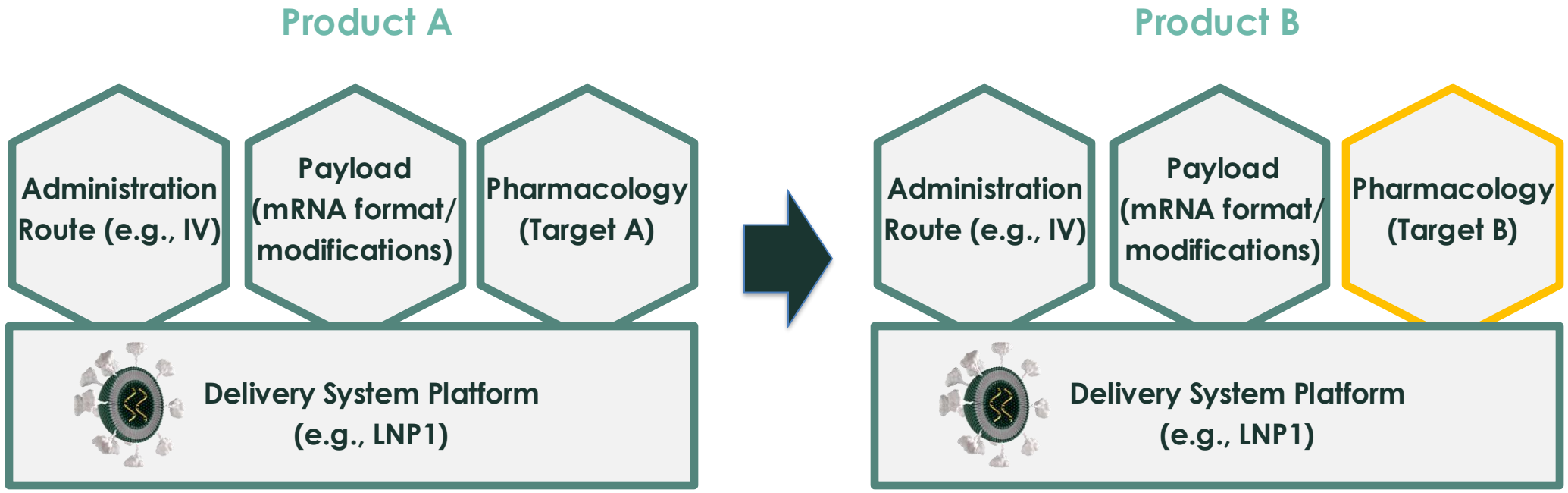
Platform Approach

LNP are Highly Adaptable to a Platform Technology Approach



Standard characterization package

Streamlined package

- Can we leverage distribution and safety information on payload and delivery platforms to streamline development programs?

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Summary

- LNP can be administered repeatedly without changes in the pharmacodynamic, pharmacokinetic or toxicity profiles
- LNP toxicity is predictable, dose-related and monitorable, and effects resolve within 7-10 days
- Pharmacokinetics and distribution are governed by the LNP, not the payload
- No delivery in germline cells
- LNP are highly adaptable to a platform technology approach to product development

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