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Abstract 258:

Phase I/IIa Study of TT-034, a DNA-Directed RNA Interference (ddRNAi) Agent Delivered as a Single Administration for the Treatment of Subjects with Chronic Hepatitis C Virus (HCV)

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Today's presentation includes forward-looking statements intended to qualify for the Safe Harbor from liability established by the Private Securities Litigation Reform Act of 1995. These forward-looking statements, including statements regarding our planned pre-clinical studies and clinical trials, regulatory approval process and demand for our product candidates, are subject to risks, uncertainties and other factors that could cause actual results to differ materially from those suggested by our forward-looking statements.

These factors include, but are not limited to, the following: we have incurred significant net losses and anticipate that we will continue to incur significant net losses for the foreseeable future; we have never generated any revenue from product sales and may never be profitable; we will need to raise additional funding in the future, which may not be available on acceptable terms, or at all; no product candidates utilizing ddRNAi technology have been approved for commercial sale in the United States, and our approach to the development of ddRNAi technology may not result in safe, effective or marketable products; we are early in our product development efforts and may not be able to obtain regulatory approvals for the commercialization of some or all of our product candidates; our ability to develop and successfully commercialize product candidates may be compromised by other companies developing their technologies or product candidates for our target indications more rapidly than we do or if their technologies are more effective; we may not be able to obtain exclusivity or intellectual property rights for our product candidates or prevent others from developing similar competitive products; issues may arise that impact ddRNAi delivery into the cells and limit our ability to develop and commercialize product candidates.

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Benitec Pipeline Programs

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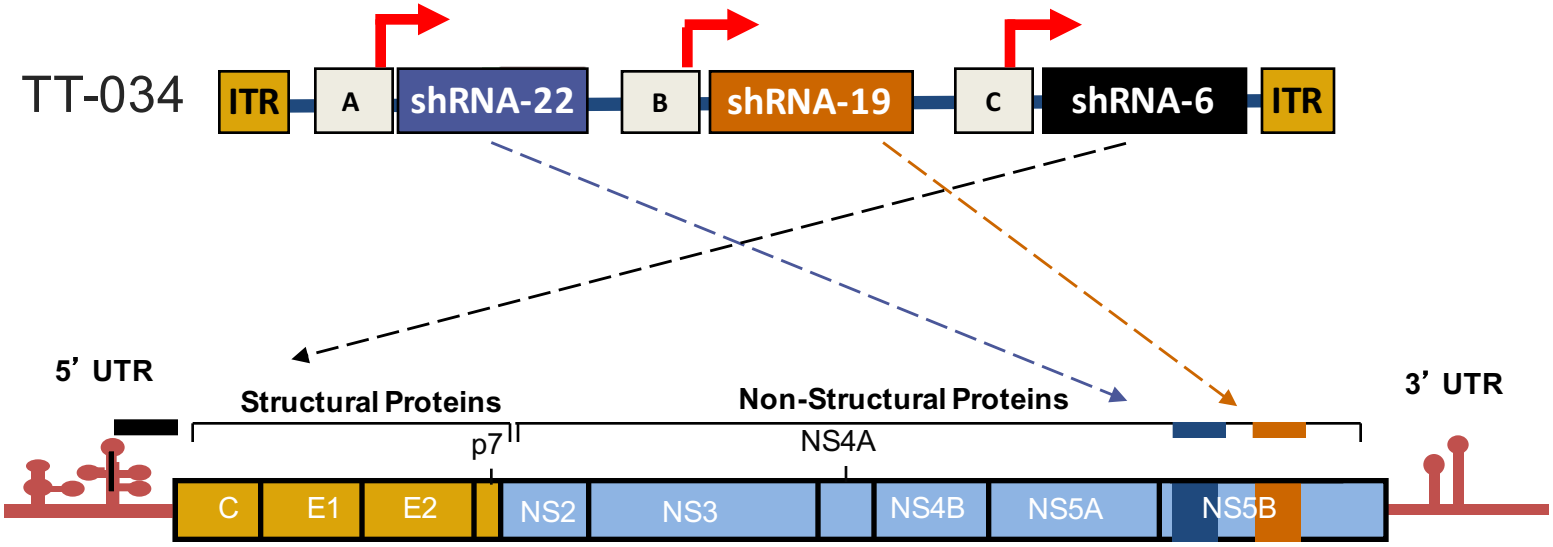
Program	Discovery	Preclinical	IND-Enabling	Phase I/II	Phase III	Status
Infectious Disease						
Hepatitis C *TT-034*						• Nine patients dosed • Program terminated February 2016 • Safe and well tolerated • All patients dosed will be followed to study completion
Hepatitis B *BB-HB-331*						• In vitro POC completed • In vivo POC underway
Ocular Disease						
AMD *BB-AMD-233*						• Screening for vector with pan-retinal delivery following intravitreal injection
Genetic Disease						
OPMD *BB-OP-1-31*						• Finalization of clinical candidate in process

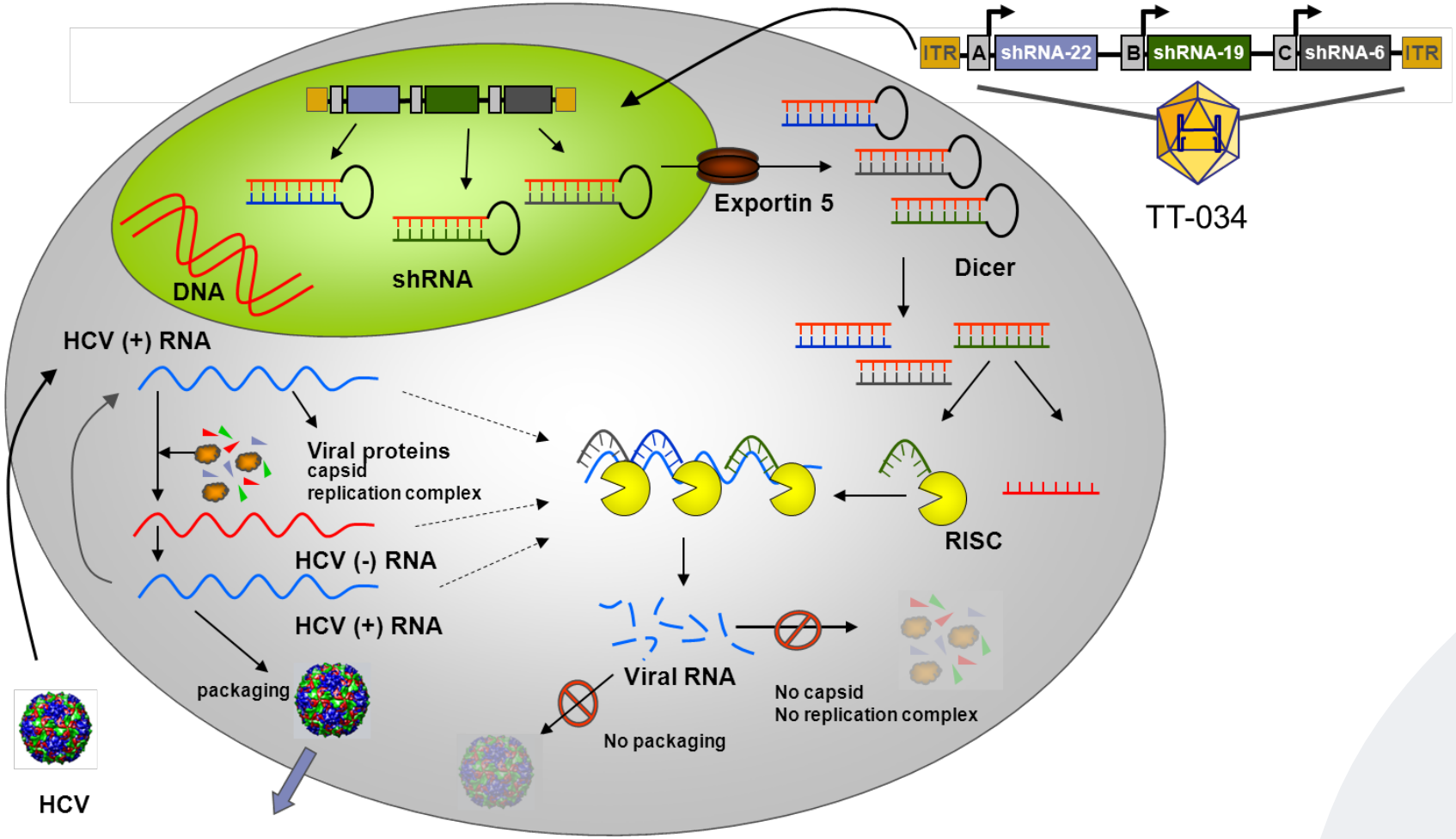
Overview of HCV

- Hepatitis C is a complex public health problem, characterized by:
  - High prevalence of chronic infection by an RNA virus
  - Increasing burden of HCV-associated disease
  - Low rates of testing and treatment
  - Prospect of increasing incidence associated with injectable drug abuse
- According to the WHO, over 170 million individuals worldwide have chronic hepatitis C
- Chronic infection can result in cirrhosis and death in 20% of patients due to end-stage liver disease or hepatocellular carcinoma
- HCV predominantly infects and replicates within hepatocytes, though some studies have shown evidence to suggest extrahepatic replication

TT-034: Expression of Multiple Therapeutic Agents from a Single Vector

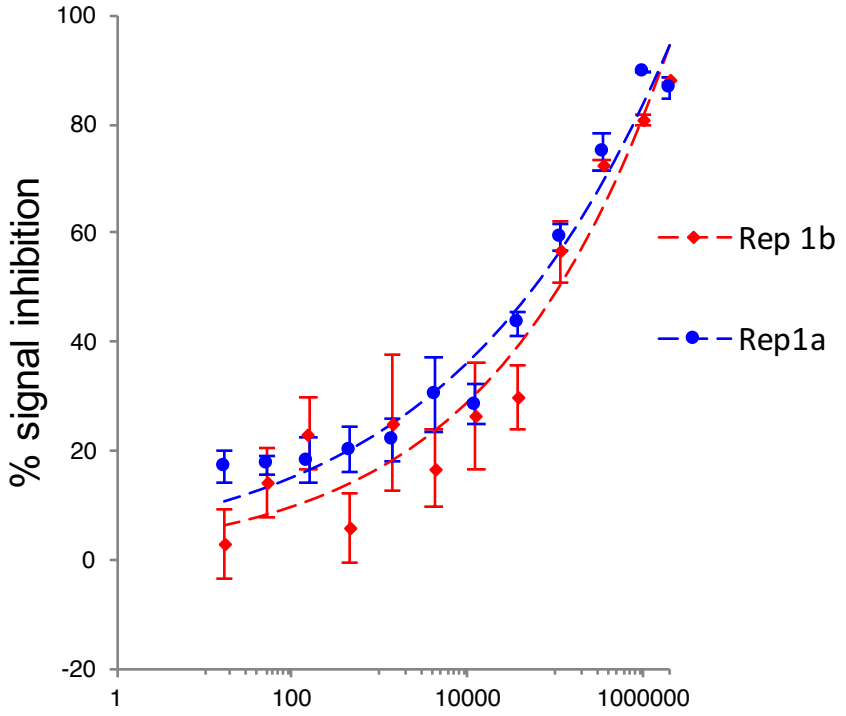


- Three independently transcribed RNAi elements target 3 separate, well-conserved regions of the HCV genome; helps prevent the generation of viral escape mutants
- For non-viral diseases, the ability to produce multiple therapeutic shRNA allows for targeting multiple genes in different pathways

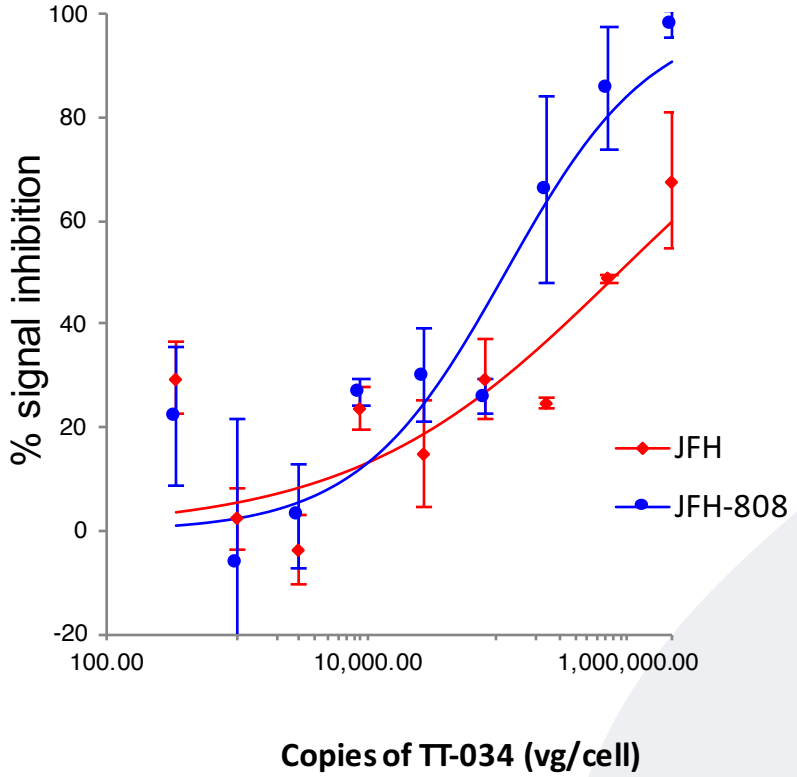


Dose Dependent Activity Against HCV Replicon and Infectious Tissue Culture System

HCV replicon inhibition



HCV inhibition in cell culture (HCVcc)



TT-034: AAV Delivery

Wildtype AAV8

REP/CAP removed and replaced with expression cassette

TT-034

Recombinant AAV8 - HCV

- Non-integrating, non-pathogenic viral delivery system
- To date, AAV has been used in 137 clinical trials with excellent safety record*
- Sustained expression (months/years) following single injection
- Complete transduction of liver hepatocytes with serotype 8 (AAV8)

* http://www.abedia.com/wiley/vectors.php

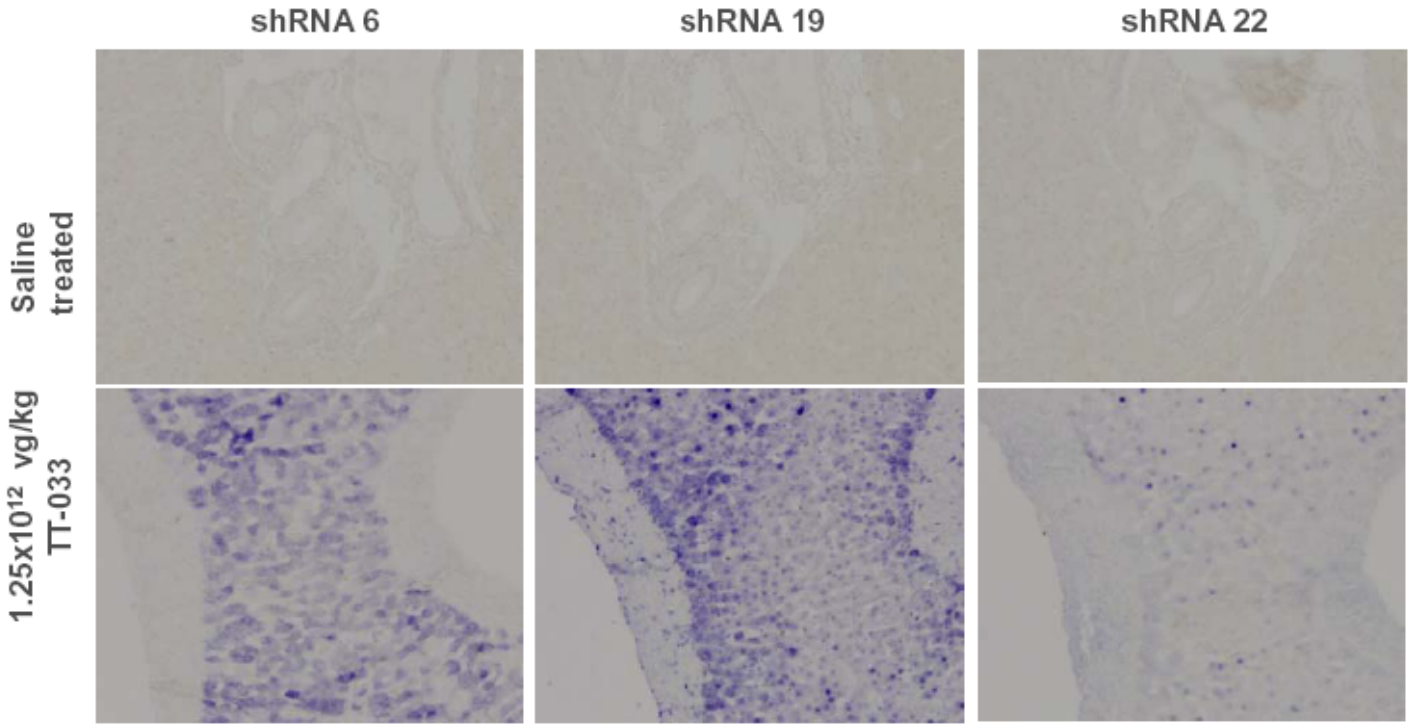
TT-034: AAV8 Permits Complete Hepatocyte Transduction in Non Human Primates

animal	SSAN3 Female	
dose	1.25 E12 vg/kg	
	copies per cell	
TISSUE	mean	sd
Liver-LT-Caudal	199.6	43.9
Liver-RT-Caudal	165.2	29.9
Liver-Medial	142.8	14.5
Spleen	23.7	0.7
LN-Inguinal	15.9	0.6
LN-Mandibular	13.2	0.8
Injection Site	7.3	1.4
Bone Marrow	3.4	0.1
LN-Mesenteric	2.5	0.0
Kidney	1.0	0.1
Heart-LT Ventricle	1.0	0.0
Heart-RT Ventricle	0.4	0.0
Thyroid	0.3	0.1
Lung	0.3	0.0
Cecum	0.3	0.0
Jejunum	0.2	0.0
Heart-Septum	0.2	0.0
Ileum	0.1	0.0
Duodenum	0.1	0.0
Colon	0.1	0.0
Ovary	0.1	0.0
Brain-Diencephelon	0.1	0.0
Pancreas	0.0	0.0
Brain-cerebellum	0.0	0.0
Skeletal muscle	0.0	0.0
Urinary Bladder	0.0	0.0
Thymus	0.0	0.0
Rectum	0.0	0.0
Brain-Parietal	0.0	0.0
Gallbladder	Tissue NA	
Adrenals	Tissue NA	
LN-axillary	Tissue NA	

Biodistribution Analysis

> 91% detected vector in hepatic tissues

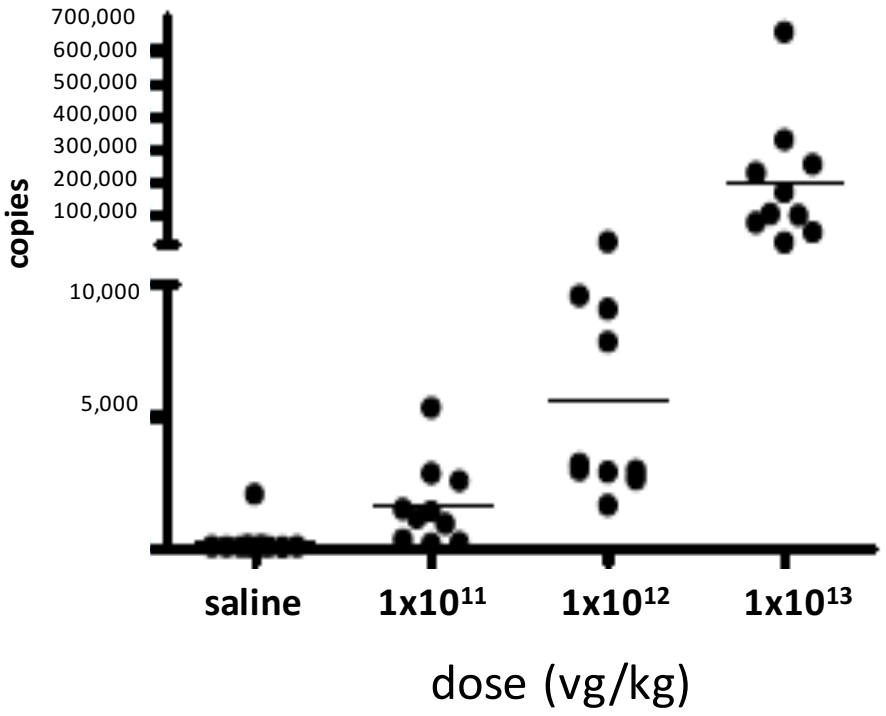
Qualitative In Situ Hybridization Analysis



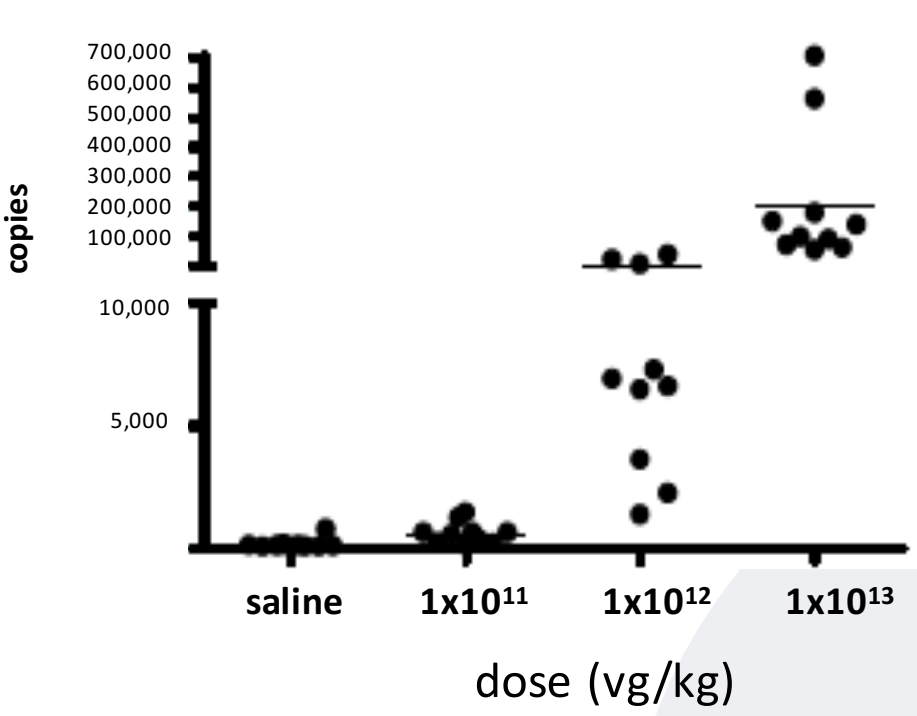
TT-034: Long Durability of shRNA Expression from a Single Administration

Levels of shRNA22 in murine hepatic tissues

60 days post dosing



180 days post dosing



From Bench to Bedside: The Regulatory Path of TT-034

- First ddRNAi applied systemically using a non-withdrawable viral vector in humans
- Oversight by FDA (CBER), NIH OBA, EMA, MHRA, AFSSAPS, & Swiss Medic
- Agencies were enthusiastic about the approach and very collaborative
- Favorable review at National Institutes of Health – Recombinant DNA Advisory Committee (RAC) meeting
- "OK to proceed" after 24 day FDA review of IND without substantial questions

Clinical Validation: Phase I/IIa study at Duke (Patel), UCSD (Wyles), & Texas Liver Institute (Lawitz), Methodist Dallas (Mantry)

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ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Safety and Efficacy Study of Single Doses of TT-034 in Patients With Chronic Hepatitis C

This study is currently recruiting participants. (see Contacts and Locations)

Verified July 2014 by Tacere Therapeutics, Inc.

Sponsor:
Tacere Therapeutics, Inc.

Information provided by (Responsible Party):
Tacere Therapeutics, Inc.

ClinicalTrials.gov Identifier:
NCT01899092

First received: July 8, 2013
Last updated: July 24, 2014
Last verified: July 2014
History of Changes

Primary Endpoints (Safety):

- Incidence of adverse events
- Changes in clinical parameters

Secondary Endpoints (Efficacy):

- Sustained reduction in HCV viral load in the blood
- Assessment of TT-034 levels in liver biopsy
- Assessment of shRNA expression in liver biopsy

Dose Escalation Schema of the TT-034 Clinical Protocol

Cohort	Intravenous Dose (vg/kg)	Dose escalation step (log 10)	Total No subjects	Dosing scheme for subjects	Observation period per subject and between cohorts before dose escalation
1	4.00×10^{10}	Starting dose	2	Sequential (1+1)	6 weeks
2	1.25×10^{11}	0.5	3	Sequential and parallel (1+2)	6 weeks
3	4.00×10^{11}	0.5	2	Sequential and parallel (1+2)	6 weeks
4	1.25×10^{12}	0.5	2	Sequential and parallel (1+2)	10 weeks
5	4.00×10^{12}	0.5	N/A*	Sequential and parallel (1+2)	10 weeks

- DSMB review after first patient in each cohort and between cohorts
- Extensive safety monitoring during 24 weeks observation
- Currently dosed both subjects in cohort 4

* Feb 2016 – Board's commercial decision to halt further development

TT-034: Primary and Secondary Endpoints in 24 Week Study

Primary Endpoints (Safety):

- Incidence of treatment-emergent adverse events
- Changes in clinical and laboratory parameters

Secondary Endpoints (Efficacy, PK, and PD):

- Change in HCV viral load
- Assessment of viral vector DNA levels in liver biopsy (Day 21)
- Assessment of shRNA expression in liver biopsy (Day 21)
- siRNA expression levels in exosomes in serum
- Blood vector DNA levels in serum

Following the initial 24 week study period, subjects are enrolled in a follow-on 4.5 year long term safety monitoring study.

Demographics of Subjects Enrolled and Dosed with TT-034 Through Cohort 3

	Total (N=7)	Cohort 1 $4.00e^{10}$ vg/kg (N=2)	Cohort 2 $1.25e^{11}$ vg/kg (N=3)	Cohort 3 $4.00e^{11}$ vg/kg (N=2)
Age (years) Mean (Min, Max)	47 (27, 64)	53 (51, 55)	44 (33,57)	45.5 (27,64)
Gender: Male (%)	86%	100%	67%	100%
BMI (kg/m^2), Mean	24.95	23.87	24.93	26.05
Race (%)				
Asian	0	0	0	0
Black or African-American	29%	50%	33%	0
White	71%	50%	67%	100%
Other	0	0	0	0

TT-034 Safety and Tolerability Through First Three Cohorts

	Total (N=7) n (%)	Cohort 1 $4.00e^{10}$ vg/kg (N=2) n (%)	Cohort 2 $1.25e^{11}$ vg/kg (N=3) n (%)	Cohort 3 $4.00e^{11}$ vg/kg (N=2) n (%)
Number of patients who experienced ≥1				
TEAE	7 (100%)	2 (100%)	3 (100%)	2 (100%)
Mild TEAEs	7 (100%)	2 (100%)	3 (100%)	2 (100%)
Moderate TEAEs	5 (71%)	1 (50%)	2 (67%)	2 (100%)
Severe TEAEs	2 (29%)	0 (0%)	2 (67%)	0 (0%)
Drug-related TEAE	1 (14%)	1 (50%)	0 (0%)	0 (0%)
Drug-related moderate or severe TEAEs	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Treatment-emergent SAE	1 (14%)	0 (0%)	1 (33%)	0 (0%)
Drug-related treatment-emergent SAE	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Data in database as of 03 May, 2016

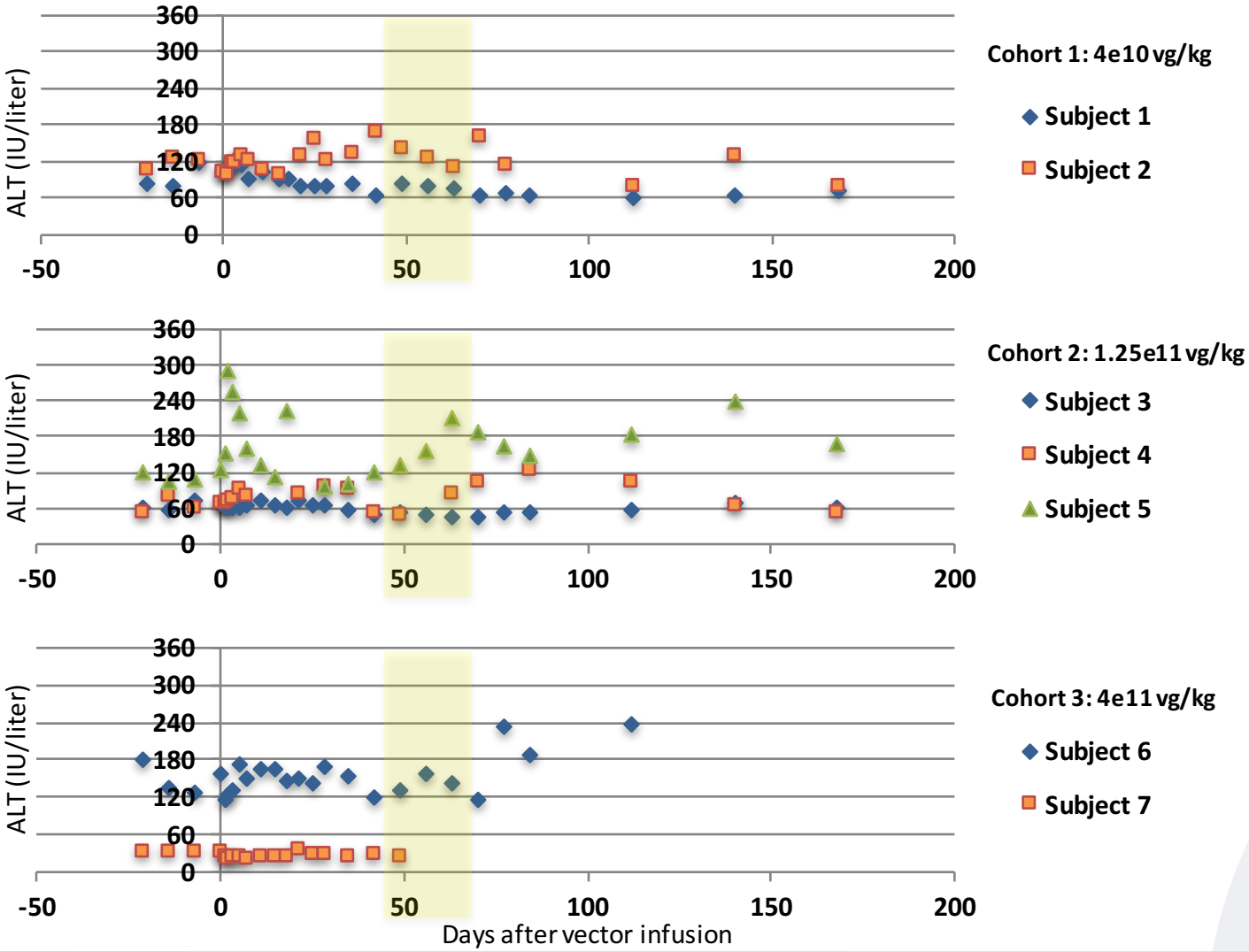
AE = adverse events
n = number of patients with an observation
N = number of patients in the safety population
SAE = serious adverse events
TEAE = treatment-emergent adverse events

The most common AE, headache, was reported in 3 subjects. Contusion, nasopharyngitis, URI and nausea were each reported in 2 subjects.

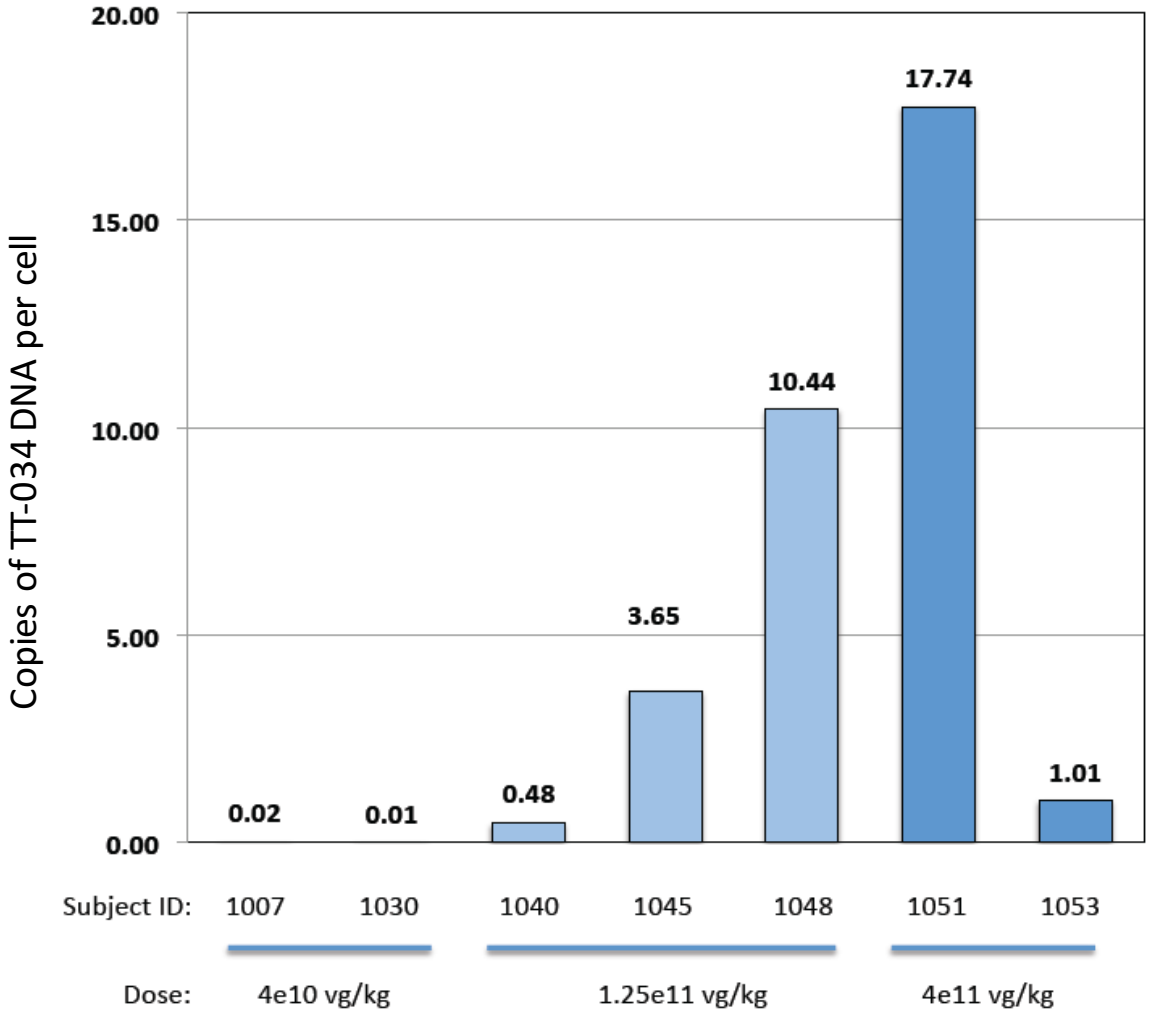
Summary of Adverse Events Graded as Moderate or Severe

	Grade	Relationship to Study Drug
Preferred Term		
001007		
Decreased appetite	Grade 2 (Moderate)	Not related
Pain in extremity	Grade 2 (Moderate)	Unlikely related
001045		
Rib fracture	Grade 3 (Severe)	Not related
Pulmonary embolism	Grade 3 (Severe)	Unlikely related
Encephalopathy	Grade 2 (Moderate)	Unlikely related
Tooth fracture	Grade 2 (Moderate)	Not related
Weight Loss	Grade 2 (Moderate)	Unlikely related
Aspartate aminotransferase increased	Grade 3 (Severe)	Unlikely related
Pruritis	Grade 2 (Moderate)	Unlikely related
Febrile Disorder	Grade 2 (Moderate)	Not related
001048		
Weight increased	Grade 2 (Moderate)	Not related
Syncope	Grade 3 (severe)	Unlikely related
001051		
Photosensitivity	Grade 2 (Moderate)	Not related
001053		
Headache	Grade 2 (Moderate)	Not related

No Evidence for T-Cell Capsid Response at Doses Up to 4e11 vg/kg

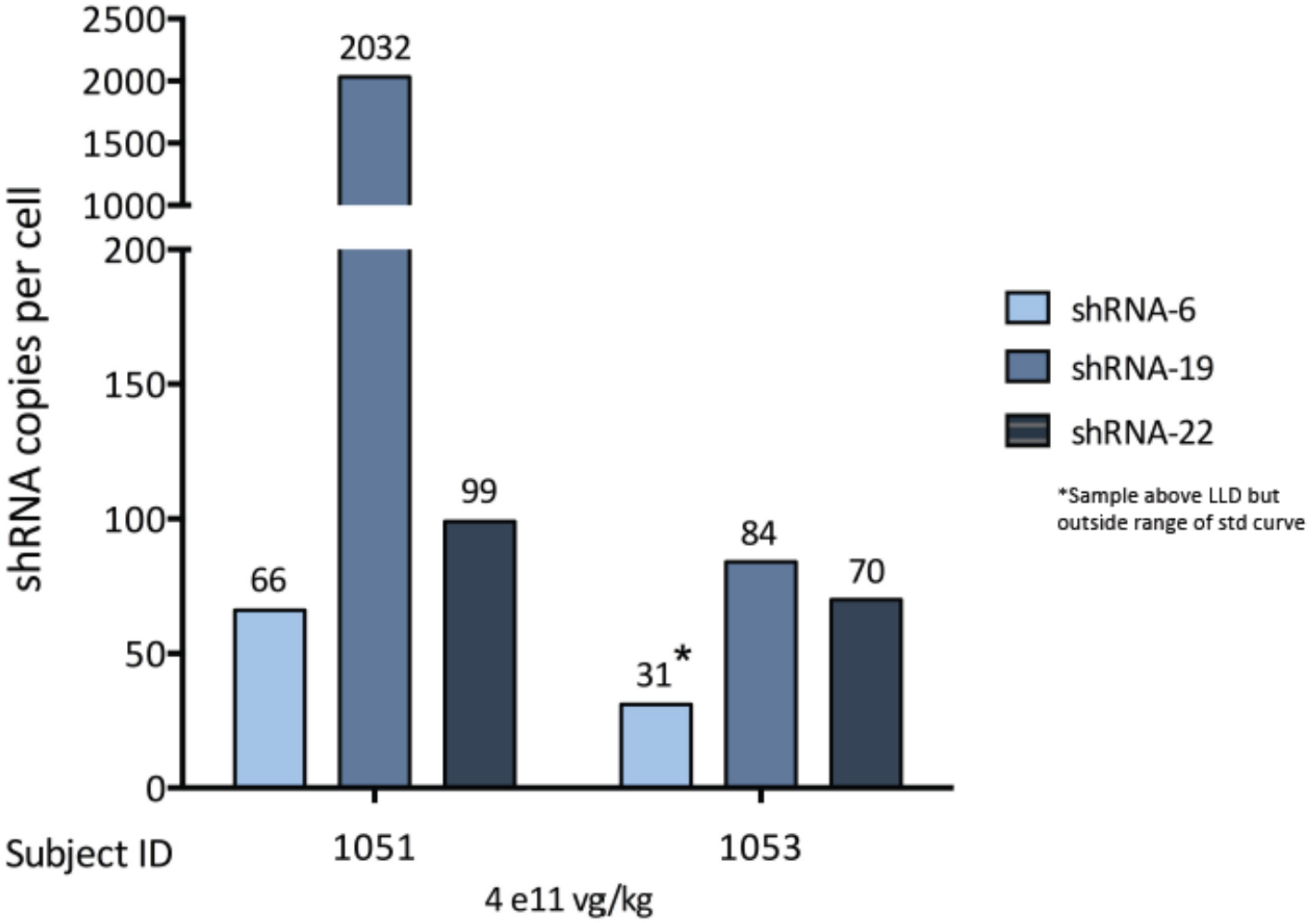


Hepatic DNA Levels in Biopsies Taken From TT-034 Treated Subjects



Liver biopsies collected
~ Day 21 post dosing

shRNA Expression Levels in Biopsies Taken From TT-034 Treated Subjects

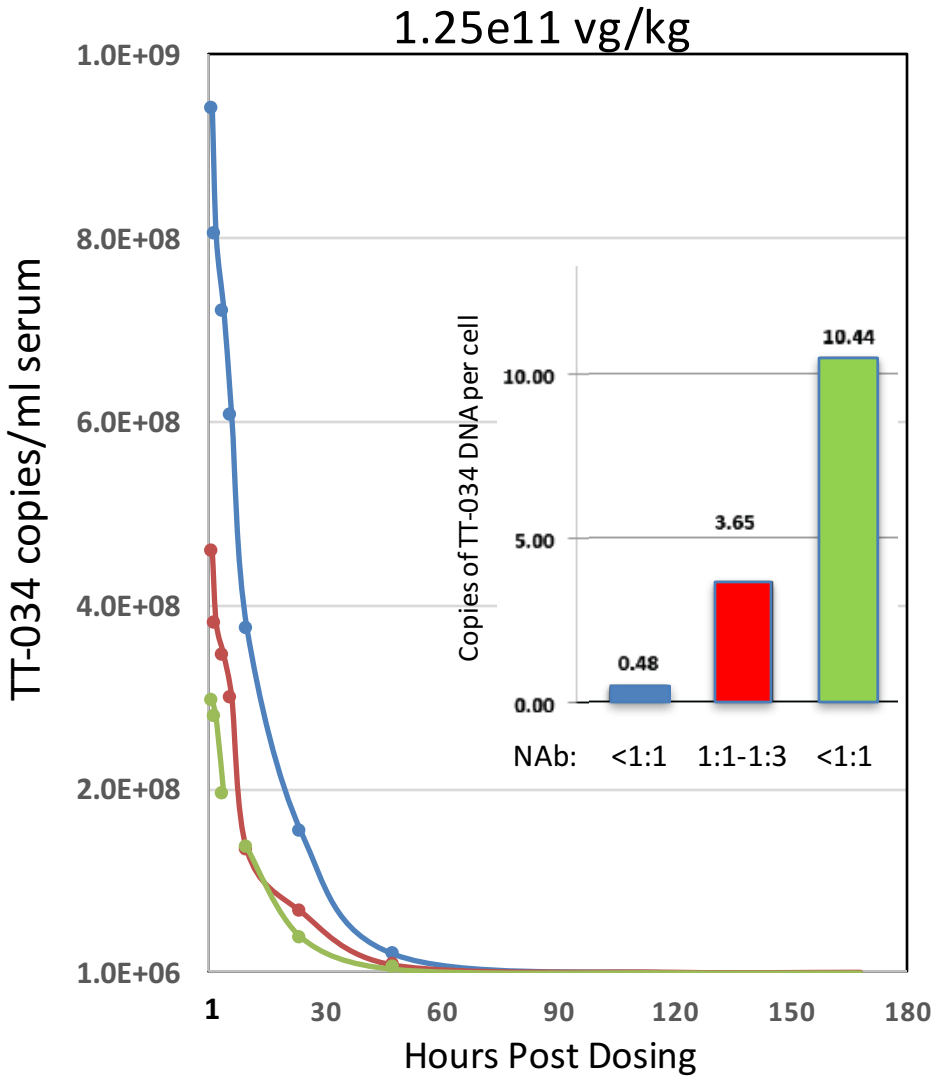


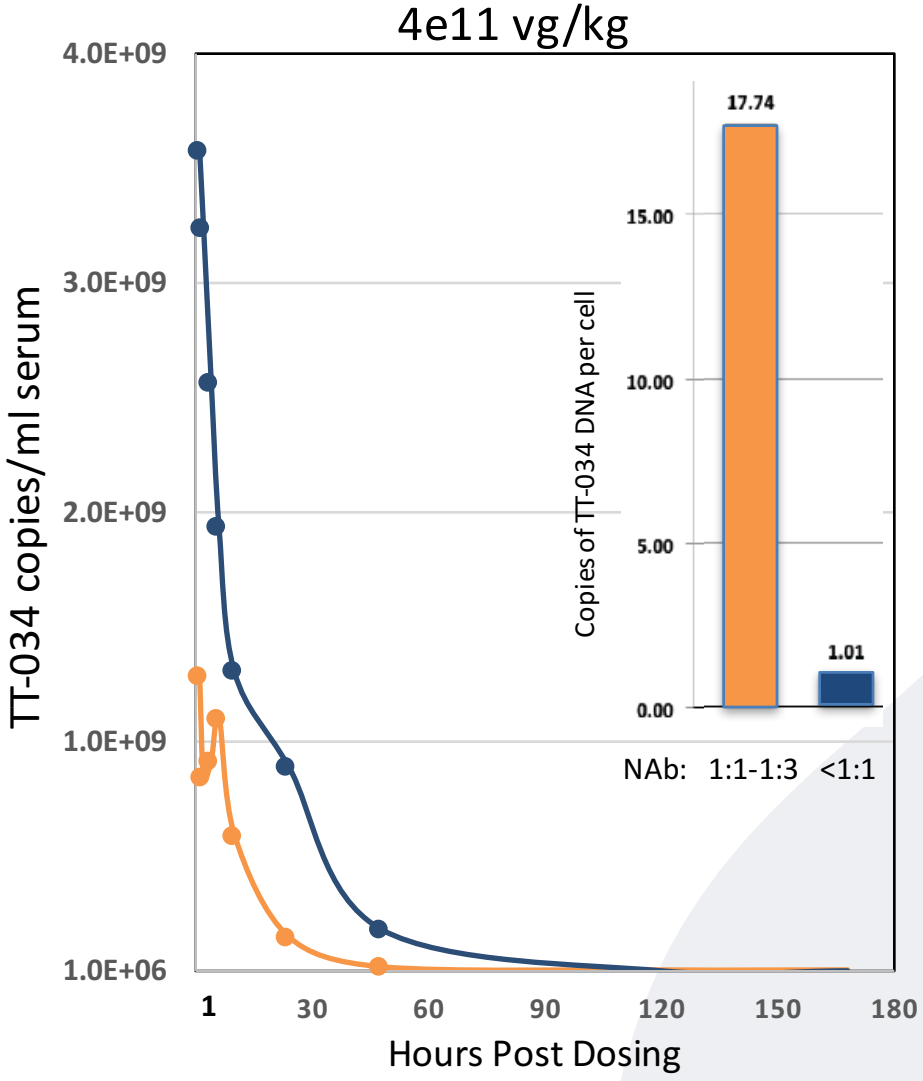
PK and Shedding from TT-034 Treated Subjects

cohort dose administered	Cohort 1 4e10 vg/kg		Cohort 2 1.25e11 vg/kg			Cohort 3 4e11 vg/kg	
Subject ID	1007	1030	1040	1045	1048	1051	1053
collection time	TT-034 copies / ml serum		TT-034 copies / ml serum			TT-034 copies / ml serum	
pre-dose	< LLD	< LLD	< LLD	< LLD	< LLD	< LLD	< LLD
1 hour	9.13E+07	1.61E+08	9.42E+08	4.59E+08	2.97E+08	1.28E+09	3.57E+09
2 hours	1.97E+07	6.80E+07	8.04E+08	3.81E+08	2.78E+08	8.37E+08	3.24E+09
4 hours	1.36E+06	1.97E+07	7.21E+08	3.45E+08	1.93E+08	9.14E+08	2.56E+09
6 hours	5.98E+05	7.24E+06	6.07E+08	3.00E+08	no sample	1.10E+09	1.93E+09
10 hours	2.93E+05	2.10E+06	3.74E+08	1.32E+08	1.36E+08	5.87E+08	1.30E+09
24 hours	5.65E+04	3.85E+05	1.53E+08	6.56E+07	3.84E+07	1.44E+08	8.88E+08
48 hours	7.24E+03	1.13E+05	2.03E+07	7.63E+06	3.86E+06	1.35E+07	1.79E+08
120 hours	< LLD	> LLD, NQ	2.49E+05	1.38E+04	1.05E+05	2.78E+04	4.24E+05
168 hours	< LLD	> LLD, NQ	1.32E+05	1.01E+04	> LLD, NQ	1.66E+04	2.76E+05

- TT-034 levels spike rapidly following intravenous administration
- Vector is rapidly cleared from serum, with much of the vector cleared or transduced into tissues within 24 hours
- All collected samples from patients comprised of saliva, urine , stool and semen from male subjects revealed **no quantifiable TT-034 vector shedding** in those samples at Week 4, Week 8, Week 12, Week 16, Week 20 or at Week 24 .

Correlation of Variability in Transduction in Liver Biopsies at Day 21 with Initial Vector PK?





Summary

- TT-034 is a first in man treatment that uses ddRNAi to produce anti-HCV shRNA following intravenous delivery by AAV
- We believe this is the first time that non-withdrawable RNAi has been introduced directly into man using systemic viral administration
- The data collected through cohort 3 of the phase I/IIa study demonstrate that TT-034 is well tolerated and safe in human subjects infected with HCV.
- TT-034 can effectively transduce hepatocytes and concurrently express the three anti-HCV shRNAs
- Initial data may suggest that variability in transduction may be associated with PK data