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PRODUCT: GENGLYCOS™ (Pariglasgene brecaparvovec-opnr, DTX401)

APPLICANT: Ultragenyx Pharmaceutical, Inc.

PROPOSED INDICATION: GENGLYCOS™ is indicated to reduce daily cornstarch intake as an adjunct to nutritional management in adults and pediatric patients 8 years of age and older with glycogen storage disease type Ia (GSDIa)

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EXECUTIVE SUMMARY:

GENGLYCOS™ (pariglasgene brecaparvovec-opnr, DTX401) is a non-replicating, recombinant adeno-associated virus serotype 8 (AAV8) vector containing a codon-optimized expression cassette for the gene encoding glucose-6-phosphatase (G6Pase). GENGLYCOS™ is indicated for the treatment of pediatric and adult patients with glycogen storage disease type Ia (GSDIa; also referred to as von Gierke disease). GENGLYCOS™ is administered as a single intravenous (IV) infusion at a dose level of 1.0×10^{13} genome copies per kilogram (gc/kg) of bodyweight.

In vivo pharmacology studies conducted in 2-week-old glucose-6-phosphatase, catalytic subunit 1 (G6PC) (b) (4) demonstrated that IV administration of DTX401 at dose levels of 5.0×10^{11} or 1.0×10^{13} gc/kg led to dose-dependent increases in hepatic G6Pase activity and fasting glucose levels. At the higher dose level of 1.0×10^{13} gc/kg, DTX401 also improved non-fasting blood glucose, cholesterol, and triglyceride levels, and normalized fasting glucose and the hepatomegaly and nephromegaly characteristic of (b) (4) mice to levels seen in wildtype (WT) mice. The minimally effective dose identified in these studies is equivalent to 9.0×10^{11} gc/kg of GENGLYCOS™. These data provide confirmatory mechanistic evidence in support of the effectiveness of DTX401.

Three separate 92-day, single-dose toxicology studies were conducted in healthy adult and juvenile mice. In adult mice, the no observed adverse effect level (NOAEL) for IV administration of DTX401 was 1.0×10^{13} gc/kg, based on findings of single-cell hepatic necrosis and Kupffer cell hypertrophy/hyperplasia at higher dose levels. In juvenile mice administered IV DTX401 on postnatal days (PNDs) 2, 14, or 28, the NOAEL was 7.0×10^{13} gc/kg. Decreasing levels of vector DNA were observed over time in the livers of mice administered DTX401 at PND 28 or younger. One 6-month, single-dose toxicology study was conducted in healthy juvenile non-human primates (NHPs) and identified a NOAEL equivalent to 1.3×10^{14} gc/kg of GENGLYCOS™.

Following IV administration in mice, DTX401 biodistribution (BD) was highest in the liver and vector DNA was detected in all evaluated tissues, including the ovaries and testes, where both DTX401 DNA and RNA were detected. Intravenous administration of DTX401 at 7×10^{13} gc/kg to male or female mice prior to mating had no impact on clinical outcomes in offspring and did not result in detection of DTX401 DNA in offspring livers. Similarly, IV administration of DTX401 at 7×10^{13} gc/kg to pregnant dams at presumed gestational day (GD) 6 resulted in DTX401 DNA detection in placenta but not offspring livers, and there was no impact on embryofetal development on GD 18.

PHARMACOLOGY/TOXICOLOGY RECOMMENDATION:

There are no nonclinical deficiencies in the pharmacology/toxicology studies and there are no outstanding requests for additional nonclinical data. The nonclinical data provided in this submission support the approval of this biologics license application.

Formulation and Chemistry:

GENGLYCOS™ (pariglasgene breccaparovvec-opnr) is a non-replicating, recombinant AAV8 vector encoding human G6Pase. The drug substance (DS) is manufactured by (b) (4)

(b) (4) The DS is stored (b) (4) GENGLYCOS™ encodes a codon-optimized version of the wildtype human G6PC coding sequence (b) (4)

(b) (4) The expression cassette contains (b) (4) the native human G6PC promoter and enhancer (GPE) elements. The GPE elements were included to mimic the endogenous transcriptomic response to metabolic and hormonal signaling.

The GENGLYCOS™ drug product (DP) is formulated in 20 mM Tris, (b) (4) magnesium chloride (MgCl_2), 200 mM sodium chloride (NaCl), 0.01% (w/v) poloxamer 188 at a target product concentration of 3.0×10^{13} gc/mL and a target pH of (b) (4). DP is filled into (b) (4) (8 mL) glass vials at 2 mL/vial and stored at $\leq -60^\circ\text{C}$. The recommended dose of GENGLYCOS™ is 1.0×10^{13} gc/kg body weight.

Abbreviations

AAV	Adeno-associated virus
Ab	Antibody
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate aminotransferase
BD	Biodistribution
BLOD	Below the level of detection
(b) (4)	
DNA	Deoxyribonucleic acid
DP	Drug product
DRG	Dorsal root ganglia
DS	Drug substance
(b) (4)	
G6Pase	Glucose-6-phosphatase
G6PC	Glucose-6-phosphatase catalytic subunit 1
gc	Genome copies
GD	Gestational day
GLDH	Glutamate dehydrogenase
GPE	Glucose-6-phosphatase promoter and enhancer
GSDIa	Glycogen storage disease type Ia
HCA	Hepatocellular adenoma
HEK	Human embryonic kidney
IFN- γ	Interferon- γ
IL-10	Interleukin 10
IL-12p70	Interleukin 12p70
IL-6	Interleukin 6
IV	Intravenous
kg	Kilogram
mg	Miligram
min	Minute
mL	Mililiters
mM	Milimolar
nAb	Neutralizing antibody
NHP	Non-human primate
Nmole	Nanomole
NOAEL	No observed adverse effect level
(b) (4)	

(b) (4)	
PND	Postnatal day
(b) (4)	
RNA	Ribonucleic acid
TBIL	Total bilirubin
vp	Vector particles
WT	Wildtype
w/v	Weight by volume
µg	Microgram

Related File

CBER IND #17965; Ultragenyx Pharmaceutical Inc; Adeno-associated virus (AAV) Serotype 8 (AAV8) vector expressing Human Glucose-6-Phosphatase-Alpha [DTX401]

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INTRODUCTION

GENGLYCOST™ (pariglasgene breccaparovvec-opnr, DTX401) is a non-replicating, recombinant AAV8 vector-based gene therapy indicated for the treatment of GSDIa. GSDIa is an autosomal recessive inborn error of metabolism caused by a genetic deficiency of microsomal G6Pase- α . This leads to impaired glucose production and glycogen accumulation in the liver and kidneys. GSDIa patients present with severe hypoglycemia and seizures within the first months of life.

Lifelong consumption of uncooked cornstarch (Glycosade®) every few hours, including overnight, is required to maintain stable blood glucose levels and prevent life-threatening hypoglycemia. Patients also require a comprehensive nutritional plan to minimize intake of simple sugars while ensuring provision of required nutrients. Despite these measures, patients remain at risk for progressive liver and kidney dysfunction and at increased risk of liver tumors and malignancies. There are no approved disease-modifying therapies for GSDIa.

GENGLYCOS™ is a one-time therapy intended to provide exogenous G6PC1 to hepatic cells to produce G6Pase- α and correct the underlying metabolic dysfunction in GSDIa. GENGLYCOS™ contains an expression cassette encoding codon-optimized human G6Pase- α under the control of the endogenous human GPE sequences. G6Pase- α is an isozyme of G6Pase and these terms are used interchangeably throughout this memo.

NONCLINICAL STUDIES

The product was referred to as DTX401, AAV8-coG6PC, and AAV8-GPE throughout the Applicant's nonclinical development. The earlier versions of the product evaluated in Studies #1-4 do not contain the (b) (4) of DTX401 but support the activity of DTX401 as they encode the same protein product.

Note: The Applicant initially evaluated titers of DTX401 using (b) (4) which was later replaced with a (b) (4) method. A conversion factor of (b) (4) is applied to convert (b) (4) titers to (b) (4) equivalents. Regardless of which method was used, dose levels were reported in (b) (4) equivalents in nonclinical study reports and in this memo.

PHARMACOLOGY STUDIES

Summary List of Pharmacology Studies

The following pharmacology studies were conducted to support the rationale for the administration of pariglasgene breccaparovvec-opnr for the proposed clinical indication.

In Vitro Studies

No in vitro pharmacology studies were performed with DTX401.

In Vivo Studies

In Vivo Studies in (b) (4) Animals

Study Number	Study Title / Publication Title	Report Number / Citation
1	(b) (4)	(b) (4)
2	(b) (4)	(b) (4)

Study Number	Study Title / Publication Title	Report Number / Citation
3	(b) (4)	(b) (4)
4	(b) (4)	(b) (4)
5	DTX401: Proof of concept and candidate selection	DTX15-401-1

In Vivo Studies in Healthy Animals

Study Number	Study Title / Publication Title	Report Number
6	In vivo potency study with DTX401 interim reference standard in C57BL/6 mice	WOO17-01
7	In vivo potency study for DTX401 in C57BL/6 mice	WOO17-07

Note: Studies #2-7 are summarized in this review memo under ‘Overview of Pharmacology Studies.’ Studies #1 and #3 are not summarized in this review memo because they contain data redundant to Studies #2 and #5.

Overview of Pharmacology Studies

Overview of In Vivo Studies

In vivo pharmacology studies were conducted in (b) (4) mice. The (b) (4) mouse model contains a (b) (4), leading to catalytic inactivation of G6Pase (b) (4). The model is associated with high early mortality at weaning and mimics features of human GSDIa including hypoglycemia, growth retardation, hepatomegaly, and nephromegaly ((b) (4)).

In Vivo Studies in (b) (4) Animals

Study #2 (b) (4)

Objective: To evaluate the impact of a single IV administration of DTX401 on model-related outcomes in (b) (4) mice.

Methods and Key Results:

- 2- or 4-week-old (b) (4) mice (n=18 total) were IV administered DTX401 at dose levels ranging from 5×10^{12} to 3×10^{13} vector particles (vp)/kg. One 15-week-old and one 30-week-old mouse were also administered DTX401. Age-matched wildtype or heterozygous animals were used as controls. All mice were sacrificed at 70-90 weeks of age to evaluate histological and metabolic outcomes.
- At 70-90-weeks of age, animals were sacrificed following a 24-hour fast. All DTX401-administered mice survived to the end of the study. Mice administered DTX401 had 3-

128% normal hepatic G6Pase- α activity and were stratified into three groups for further analysis based on activity level (3-9%, 22-63%, and 81-128%). The level of hepatic G6Pase- α activity correlated linearly with the level of transgene mRNA expression and vector copy number per cell.

- Following a 24-hour fast, DTX401-administered mice with $\geq 81\%$ of normal hepatic G6Pase- α activity had normal blood glucose and mice with 3-63% of normal levels were able to maintain euglycemia. Terminal liver weights were normalized in animals with $\geq 22\%$ normal hepatic G6Pase- α activity. The amount of hepatic glycogen in DTX401-administered mice decreased with increasing levels of hepatic G6Pase- α activity
- Glucose-6-phosphate uptake by liver microsomes prepared from these animals improved proportionally to the level of hepatic G6Pase- α activity.
- At sacrifice, no DTX401-administered mice showed evidence of hepatocellular adenoma (HCA) by ultrasound or histological analysis.

Reviewer comments:

- *This study supports sustained activity of DTX401 over 1-year post-administration.*
- *To support their position that DTX401 administration (b) (4), the Applicant cited data from a conditional, liver-specific, mouse G6pc (b) (4) line in which 17/17 mice developed liver nodules within 18 months of (b) (4) induction. Please see the reviewer comment for Study #4 for additional discussion.*

Study #4 (b) (4)

Objective: To evaluate the impact of a single IV administration of DTX401 on model-related adverse hepatocellular outcomes in (b) (4) mice.

Methods and Key Results:

- 2-week-old (b) (4) mice were IV administered either 6×10^{12} vp/kg DTX401 (b) (4) version of the product at either (b) (4) 6×10^{12} vp/kg (n=8-9/group). Mice were sacrificed between 66 and 88 weeks of age to evaluate hepatic G6Pase- α activity and liver pathology, including the formation of hepatic tumors.
- G6Pase- α activity in (b) (4) mice administered either test article ranged from 1.5 to 56 units; age-matched wildtype mice had a mean of 171.4 units of G6Pase- α activity.
- No hepatic tumors developed in the 15 animals with G6Pase- α activity at levels 3-33% of wildtype (5-56 units). Of the 11 mice with lower levels (≤ 4.1 units; 0.9-2.4% of wildtype) of G6Pase- α activity, 3 developed hepatic tumors.

Reviewer comments:

- *This study provides preliminary evidence that higher relative levels of G6Pase- α activity following gene therapy may reduce hepatic tumor development.*

- Due to the small number of animals and variable age at sacrifice, it is unclear whether the 3% wildtype levels of G6Pase- α activity that demonstrated (b) (4) activity in this study and in Study #2 translates to (b) (4) activity. Further, interspecies differences in enzymatic activity threshold may impact clinical translation (Brooks et al., 2018).

Study #5

Report Number		DTX15-401-1
Date Report Signed		No signature
Title		DTX401: Proof of Concept and Candidate Selection
GLP Status		No
Testing Facility		(b) (4)
Objective(s)		To evaluate the activity of AAV8s encoding G6Pase with (b) (4) codon optimization (b) (4) in (b) (4) mice.
Study Animals	Strain/Breed	Male and female (b) (4)
	Species	(b) (4)
	Age	10 $\pm$ 2 days
	Body Weight	4-7 g
	#/group	Groups 1-9: 2-3 Group 10: 18
	Total #	48
Test Articles		AAV8-coG6PC (lot: VIG-27AUG-(b) (4)): AAV8 vector encoding codon optimized G6Pase-α catalytic subunit. This vector was selected for further development as DTX401. (b) (4) (b) (4) (b) (4)
Control Article		No control article was used in this study.
Route of Administration		IV (retro-orbital infusion)
Study Groups and Dose Levels		Group 1 – (b) (4), AAV8-co-G6PC, 5.0×10^{11} gc/kg Group 2 – (b) (4), AAV8-co-G6PC, 1.0×10^{13} gc/kg Group 3 – (b) (4), (b) (4) Group 4 – (b) (4), (b) (4) Group 5 – (b) (4), no administration Group 6 – (b) (4), (b) (4) Group 7 – (b) (4), (b) (4) Group 8 – (b) (4), (b) (4) Group 9 – (b) (4), (b) (4) Group 10 – (b) (4), no administration
Dosing Regimen		Single administration
Randomization		No
Description of Masking		Not described
Scheduled Sacrifice Time Points		Day 14

Note: Groups 3, 4 and 6-9 evaluated versions of the product that were not selected for further development. Therefore, the results from these groups are not discussed in this memo.

Key Assessments:

- Clinical observations were performed daily, and body weights and length were evaluated every 3 days from Day 0 through the end of the study.
- Blood glucose levels were evaluated on Day 0 prior to infusion, on Day 13 (unfasted), and on Days 13-14 following 4, 8, and 24 hours of fasting.
- Clinical chemistry was evaluated on Day 0 prior to infusion, and on Day 14 at sacrifice.
- Terminal evaluations consisted of necropsy, liver and kidney organ weights, and microscopic and macroscopic evaluation of a subset of organs and tissues.
- Vector DNA (b) (4) and G6Pase- α activity were evaluated in the liver.

Key Results:

- There was no unexpected mortality in the study.
- Administration of DTX401 at 1.0×10^{13} gc/kg, but not 5.0×10^{11} gc/kg, led to improved body weight gain in (b) (4) mice.
- (b) (4) mice administered DTX401 at 5.0×10^{11} gc/kg were able to maintain low, but relatively stable blood glucose levels across the 24-hour fast. (b) (4) mice administered the higher dose level of 1.0×10^{13} gc/kg maintained a blood glucose profile similar to healthy (b) (4) mice during a 24-hour fast. Fourteen days post-administration, mice administered DTX401 at 1.0×10^{13} gc/kg had unfasted blood glucose, cholesterol, and triglyceride levels similar to (b) (4) mice.
- (b) (4) mice have enlarged livers and kidneys, which was normalized at the 1.0×10^{13} gc/kg dose level. Model-related hepatocellular swelling was reduced in a dose-dependent manner by DTX401 administration.
- There were dose-dependent increases in DTX401 DNA in the liver. G6Pase- α activity in the liver was 200 nmole/mg/min in (b) (4) mice and was not detected in the single non-administered (b) (4) animal evaluated. Administration of DTX401 led to 3.2% and 180% of wildtype activity levels at the lower and higher dose levels, respectively.

Reviewer comments:

- *Administration of DTX401 led to dose-dependent amelioration of disease-related findings in (b) (4) mice. The minimum effective dose from this study was 5.0×10^{11} gc/kg, equivalent to 9.0×10^{11} gc/kg using the final (b) (4) method for titer determination.*

Study #6 (Study WOO17-01)

In vivo potency study with DTX401 interim reference standard in C57BL/6 mice

(b) (4)

Methods and Key Results:

(b) (4)

Reviewer comments:

(b) (4)

Study #7 (Study WOO17-07)**In vivo potency study for DTX401 in C57BL/6 mice**

(b) (4)

SAFETY PHARMACOLOGY STUDIES**In Vitro Studies**

No in vitro safety pharmacology studies were performed with DTX401.

In Vivo Studies

Relevant safety pharmacology endpoints (respiratory, cardiological, and neurological endpoints) were evaluated in Study #11 and are reviewed as part of that study.

PHARMACOKINETIC STUDIES

Vector biodistribution analyses were conducted in C57BL/6 mice and NHPs as part of toxicology studies (Studies #8, 9, and 11). Therefore, these data are summarized with the respective studies.

TOXICOLOGY STUDIES**Summary List of Toxicology Studies**

The following toxicology studies were conducted to evaluate the safety of DTX401 following administration in various animal species.

Toxicology Studies:

Study Number	Study Title / Publication Citation	Report Number
8	DTX401: Single Dose Intravenous Toxicity and Biodistribution Study in C57BL/6N Mouse	VPT4185
9	A Single Dose Juvenile Toxicity Study of DTX401 in C57BL/6N Mice	DTX401-21-0007
10	A 3-Month Single Dose Toxicity Study of DTX401 by Intravenous Injection in Mice	DTX401-22-0009
11	A 6 Month Single Dose Intravenous Pharmacology and Toxicology Study of DTX401 in Cynomolgus Monkeys	DTX401-22-0006

Developmental and Reproductive Toxicology Studies:

Study Number	Study Title / Publication Citation	Report Number
12	An Embryo-fetal Development Study of DTX401 by Intravenous Injection in Mice	DTX401-23-0004
13	A Germline Transmission Study in Offspring of Mice Following a Single Intravenous Dose of DTX401 in Mice	DTX401-23-0006

Note: Study #10 is summarized briefly in this review memo as shedding data from this study is referenced in the product label.

Genotoxicity Studies:

Per the applicant, studies were not conducted to evaluate genotoxicity as they expect that the risk of DTX401 insertion is low. Potential vector integration was assessed in Study #13.

Carcinogenicity/Tumorigenicity Studies:

Per the Applicant, studies were not conducted to evaluate carcinogenicity/tumorigenicity for the following reasons:

- AAV8 vectors are predominantly non-integrating and persist as episomes with low likelihoods of genomic integration.

- There is a lack of significant correlation between AAV integration and hepatic tumor formation in humans (Gil-Farina et al., 2016; Kattenhorn et al., 2016). Further, DTX401 does not contain a WT AAV2 sequence that has been tentatively linked to HCC in humans (Logan et al., 2017).
- G6Pase is not a growth factor or an immune suppressor and is therefore not expected to drive tumor development or progression in this patient population with pre-existing risk for hepatic tumors (Chou et al., 2010).

Toxicology Studies

Study #8

Report Number		VPT4185
Date Report Signed		15-JAN-2024
Title		DTX401: Single Dose Intravenous Toxicity and Biodistribution Study in C57BL/6N Mouse
GLP Status		Yes (b) (4)
Testing Facility		(b) (4)
Objective(s)		To assess toxicity, immunogenicity and BD in wildtype mice following a single IV administration of DTX401.
Study Animals	Strain/Breed	Wildtype mice, C57BL/6N
	Species	(b) (4)
	Age	9-11 weeks
	Body Weight	Males: 21.4-31.9 g Females: 16.8-23.3 g
	#/sex/group	Toxicity: 15/sex/group/timepoint; 52/sex/group BD: 5/sex/group/timepoint
	Total #	476
Test Article		DTX401 (lot #PB17039)
Control Article		Vehicle (0.01% Pluronic F-68 w/v, 20 mM Tris, 200 mM NaCl, (b) (4) MgCl ₂ , pH (b) (4))
Route of Administration		IV
Description of the Administration Procedure		Test or control article was administered to the caudal (tail) vein at 7 mL/kg on Day 1.
Study Groups and Dose Levels		Group 1 – Toxicity, vehicle Group 2 – Toxicity, DTX401 2.0×10^{12} gc/kg Group 3 – Toxicity, DTX401 1.0×10^{13} gc/kg Group 4 – Toxicity, DTX401 6.5×10^{13} gc/kg Group 5 – BD, vehicle Group 6 – BD, DTX401 1.0×10^{13} gc/kg
Dosing Regimen		Single administration
Randomization		Yes
Description of Masking		Not described
Scheduled Sacrifice Time Points		Day 4, 29 or 92

Key Evaluations and Assessments:

- Clinical observations were conducted daily. Body weight and food consumption were evaluated weekly.
- Blood samples were collected at necropsy (Days 4, 29, or 92) for hematology, coagulation, and clinical chemistry. Cytokine analysis was performed approximately 4 hours post-dose (5 mice/sex/group).
- Neutralizing anti-AAV8 Abs (nAbs) were evaluated on Day 92 (7 mice/sex/group). Splenic T-cell responses were evaluated on Days 29 and 92 samples by measuring IFN- γ release using an (b) (4) assay (5 mice/sex/group).
- Brain, heart, kidney, liver, pancreas, spleen, testes and thymus weights were assessed in the toxicology groups (Groups 1-4; 10 mice/sex/group). Macroscopic and microscopic examinations were conducted on a full panel of tissues for the vehicle and 6.5×10^{13} gc/kg groups, and on a limited number of tissues for the 2.0×10^{12} gc/kg and 1.0×10^{13} gc/kg groups (10 mice/sex/group).
- A complete panel of tissues was evaluated for vector DNA and RNA at each necropsy timepoint (Days 4, 29, or 92). Vector DNA was detected through (b) (4)

Key Results:

- No DTX401-related adverse changes in mortality, clinical observations, body weight, or food consumption were observed. One male animal in the BD DTX401 group was euthanized on Day 60 due to a preputial infection which was not attributed to DTX401.
- On Day 29, leukocytosis (minimal increase in white blood cell, neutrophil, lymphocyte, monocyte, eosinophil, basophil, and large unstained cell counts) occurred in male mice administered DTX401 at $\geq 2.0 \times 10^{12}$ gc/kg. By Day 92 there was a partial or complete reversal in all altered Day 29 values. Transient leukopenia was noted in female mice in the 6.5×10^{13} gc/kg group; this finding was not attributed to DTX401 administration and values were within the historical control range.
- On Day 29, male mice administered $\geq 1.0 \times 10^{13}$ gc/kg had dose-dependent minimal to moderate elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), glutamate dehydrogenase (GLDH), and total bilirubin (TBIL). Female mice in the 6.5×10^{13} gc/kg group had minimal to mild elevations in ALT and GLDH. All findings normalized or trended toward normalization by Day 92.
- One female mouse in the 1.0×10^{13} gc/kg group had moderate to marked elevations in IFN- γ , IL-6, IL-10 and IL-12p70 levels. All other animals showed sporadic cytokine elevations that were not dose dependent.
- DTX401 administration led to detectable anti-AAV8 nAbs in all samples from groups administered DTX401. All DTX401 groups developed anti-AAV8 nAb (2.0×10^{12} gc/kg: 17,000; 1.0×10^{13} gc/kg: 11,102; 6.5×10^{13} gc/kg: 24,420); there were generally higher titers in female mice. Anti-AAV8 nAbs were only detected in a single vehicle-administered animal at a low level (titer: 25.55). In the 6.5×10^{13} gc/kg group, T-cell responses to the AAV8 peptide pool were observed in 2/10 mice on Day 29 and in 6/10 mice on Day 92. One sample from the 2.0×10^{12} gc/kg group was positive on Day 92

which was considered a spurious result. No T cell responses were noted against the G6PC peptide pool.

- Spleen weights (as a percent of total body weight) were higher in the 6.5×10^{13} gc/kg group compared to vehicle on Day 4 and Day 29 (both sexes), and on Day 92 (female). This was associated with mild to moderate hyperplasia of the spleen, mandibular lymph node, and mesenteric lymph node on Day 29 in most male and female mice in the 6.5×10^{13} gc/kg group. These findings normalized to vehicle levels by Day 92.
- Adverse liver findings were noted in male mice administered 6.5×10^{13} gc/kg of DTX401 beginning on Day 29. These consisted of minimal to mild Kupffer cell hypertrophy/hyperplasia, minimal mitotic increase, and minimal to mild multifocal single cell necrosis. Hepatocellular necrosis was associated with changes in clinical chemistry parameters indicative of mild liver injury. These findings normalized by Day 92, except for a minimal increase in mitosis in a few animals.
- Minimal neuronal degeneration in the cervical or thoracic dorsal root ganglia (DRG) was observed in male mice administered 6.5×10^{13} gc/kg of DTX401 on Day 29. This finding was not observed in female mice at either timepoint or in any mice on Day 92.
- Qualitative evaluation of spermatogenesis in the testes of male mice administered either vehicle or 6.5×10^{13} gc/kg of DTX401 showed no adverse findings.
- BD:
 - Vector DNA was detected across DTX401-administered mice samples, generally peaked on Day 4, and decreased thereafter. Vector DNA levels were highest in the liver (Day 4: 2.3×10^7 gc/ μ g DNA), followed by blood (5.4×10^6 gc/ μ g), spleen, injection site, lung (6.5×10^5 gc/ μ g), ovaries (3.5×10^5 gc/ μ g), pancreas, kidney, heart, testes (1.2×10^5 gc/ μ g DNA), and brain (2.2×10^4 gc/ μ g). In liver and injection site samples, Day 92 vector DNA levels were similar to those on Day 4 (84-104%). Vector DNA levels decreased from Day 29 to Day 92 in all other tissues.
 - Vector RNA was detected across DTX401-administered samples and generally peaked on Day 29. On Day 29, vector RNA levels were highest in the liver (6.2×10^7 copies/ μ g DNA), followed by spleen (4.6×10^4 copies/ μ g), ovaries, injection site, testes (4.6×10^3 copies/ μ g), lung, heart, pancreas, kidney, brain, and blood (1.5×10^2 copies/ μ g). By Day 92, vector RNA levels decreased in most tissues, stabilized in a few tissues (testes, lung, and heart), and increased significantly in blood, kidney, and liver (343-555%).
 - Vector DNA and RNA was detected at low levels in a few vehicle samples. This was attributed to contamination from DTX401-administered samples.

Reviewer comments:

- *This study in healthy adult mice supports the safety of a single IV administration of DTX401 at dose levels $\leq 1.0 \times 10^{13}$ gc/kg. As there were adverse liver, lymphoid, spleen and DRG findings in animals administered DTX401 at 6.5×10^{13} gc/kg, this study supports a NOAEL of 1.0×10^{13} gc/kg. This dose level is equivalent to $(b) (4) \times 10^{13}$ gc/kg using the final $(b) (4)$ method for titer determination.*

Study #9

Report Number		DTX401-21-0007
Date Report Signed		30-JUN-2023
Title		A Single Dose Juvenile Toxicity Study of DTX401 in C57BL/6N Mice
GLP Status		Yes
Testing Facility		(b) (4)
Objective(s)		To assess toxicity and BD in juvenile wildtype mice following a single IV DTX401 administration.
Study Animals	Strain/Breed	Wildtype mice, C57BL/6N
	Species	(b) (4)
	Age	2, 14, or 28 days
	Body Weight	PND 2: 1.00-1.70 g PND 14: 3.10-7.3 g PND 28: 6.60-15.2 g
	#/sex/group	10/sex/group/timepoint
	Total #	120
Test Article		DTX401 (lot #D401-500P-W21-01)
Control Article		Vehicle (same as Study #8)
Route of Administration		IV
Description of the Administration Procedure		Test or control article was administered using either the temporal vein (PND 2) or the tail vein (PND 14 and PND 28) on Day 1 of the study.
Study Groups and Dose Levels		Group 1 – PND 14, vehicle Group 2 – PND 14, DTX401 1.0×10^{13} gc/kg Group 3 – PND 14, DTX401 7.0×10^{13} gc/kg Group 4 – PND 28, DTX401 1.0×10^{13} gc/kg Group 5 – PND 28, DTX401 7.0×10^{13} gc/kg Group 6 – PND 2, DTX401 1.0×10^{13} gc/kg Group 7 – PND 2, DTX401 7.0×10^{13} gc/kg
Dosing Regimen		Single administration
Randomization		Yes
Description of Masking		Not described
Scheduled Sacrifice Time Points		Day 29 or 92

Key Evaluations and Assessments:

- Morbidity and mortality were evaluated twice a day.
- Clinical observations were performed 1 hour post administration, and daily through the end of the study.
- Body weight was measured weekly.
- Body temperature was measured 6-8 hours post-administration for Groups 1-5.
- Evaluation of the number of estrous cycles and mean cycle length was conducted on 14 consecutive days beginning on Day 78.
- Terminal evaluations consisted of hematology, clinical chemistry (Day 29 only), organ weights, quantitative spermatogenesis evaluation, histopathology, and femur length measurements. Liver and blood samples were collected for BD evaluations from mice administered vehicle or 1.0×10^{13} gc/kg of DTX401.

Key Results:

- A total of 5 mice died prior to scheduled necropsy (2 administered 1.0×10^{13} gc/kg, 3 administered 7.0×10^{13} gc/kg). No deaths were attributed to DTX401 administration, and the cause of death was undetermined.
- No DTX401-related adverse changes in clinical observations, body weight, temperature, estrous cycle parameters, or femur length were observed.
- In mice administered DTX401 on PND14, mild, non-dose-dependent increases in lymphocyte and white blood cell counts were noted in both male and female mice at dose levels $\geq 1.0 \times 10^{13}$ gc/kg on Day 29. On Day 92, there was a moderate decrease in lymphocyte and white blood cell counts in male mice administered $\geq 1.0 \times 10^{13}$ gc/kg. Minimal non-dose-dependent increases in reticulocyte counts were noted at dose levels $\geq 1.0 \times 10^{13}$ gc/kg only on Day 29, which appeared to correlate with increased hematopoietic cellularity observed in the spleen of these mice. In mice administered on PND 28, moderate, non-dose-dependent increases in white blood cell, lymphocyte, and large unstained cell counts were noted in males at dose levels $\geq 1.0 \times 10^{13}$ gc/kg along with mild increases in monocyte cell counts in both sexes at 7.0×10^{13} gc/kg on Day 29. On Day 92, moderate decreases in lymphocyte and white blood cell counts were seen in males at dose levels $\geq 1.0 \times 10^{13}$ gc/kg. In male mice administered on PND 2, mild to moderate dose-dependent decreases in lymphocytes were noted at $\geq 1.0 \times 10^{13}$ gc/kg along with a moderate decrease in monocytes at 7.0×10^{13} gc/kg on Day 92.
- In mice administered on PND 28, moderate increases in ALT and AST were noted in males at 7.0×10^{13} gc/kg on Day 29. These findings correlated with hepatocellular single cell necrosis observed in the livers of these mice.
- BD
 - Vector DNA and RNA were not detected in liver samples collected from vehicle-administered mice.
 - On Day 92, vector DNA in liver was detected at 2.9×10^5 copies/ μ g DNA in mice administered on PND 28. At the same timepoint, levels in mice administered on PND 14 and PND 2 were 6.8% and 2.0% of the PND 28 levels, respectively. Vector DNA detection in liver also decreased over time. By Day 92, vector DNA levels were ~60% and ~30% of Day 29 levels for mice administered on PND 14 and PND 28, respectively.
 - Vector DNA was detected in all 10 blood samples collected on Day 29 from DTX401 administered mice. Vector RNA was not detected in any blood samples on Day 29. Vector DNA and RNA were only detected in 1 of 13 blood samples collected on Day 92.
- In mice administered on PND 14, spleen weights on Day 29 (both absolute value and percent body weight) were elevated for males at $\geq 1.0 \times 10^{13}$ gc/kg and females at 7.0×10^{13} gc/kg. Spleen weights were 31-36% above concurrent control values. By Day 92 spleen weights were still elevated (48% above controls) for males at 7.0×10^{13} gc/kg. There was no concurrent control group for mice administered DTX401 on PND 28 or PND 2. For PND 28 mice, elevated spleen weights were noted in male mice in the 7.0×10^{13} gc/kg group compared to the 1.0×10^{13} gc/kg group on Day 29 which trended towards recovery by Day 92.

- Histopathology findings observed in mice administered DTX401 generally resolved by Day 92. In male mice administered on PND 14 at $\geq 1.0 \times 10^{13}$ gc/kg, dose-dependent minimal to mild increased hematopoiesis in spleen red pulp was noted on Day 29. In female mice administered on PND 14 at $\geq 1.0 \times 10^{13}$ gc/kg minimal increased hematopoiesis was noted on Day 29. These findings resolved by Day 92. In mice administered on PND 28, minimal hepatocellular necrosis, single cell necrosis and mixed cell infiltration was noted in male mice at $\geq 1.0 \times 10^{13}$ gc/kg and in female mice at 7.0×10^{13} gc/kg. By Day 92, minimal mixed cell infiltration in the liver was still present in 1 male mouse at 7.0×10^{13} gc/kg and in most female mice at $\geq 1.0 \times 10^{13}$ gc/kg.

Reviewer Comments:

- *This study supports the safety of a single IV administration of DTX401 in healthy juvenile mice at dose levels up to 7.0×10^{13} gc/kg. This dose level is equivalent to $(b) (4) \times 10^{14}$ gc/kg using the final $(b) (4)$ method for titer determination.*
- *Findings in this study suggest DTX401-related immune stimulation in male and female mice administered $\geq 1 \times 10^{13}$ gc/kg on PND 14 and male mice administered $\geq 1 \times 10^{13}$ gc/kg on PND 28.*
- *In the cohorts where hepatic vector DNA levels were evaluated over time (PND 14 and PND 28), there was a notable decline. No decline in hepatic vector DNA levels was noted in Study #8, in which 9-11-week-old mice received IV administration of the same dose level (1.0×10^{13} gc/kg). Together, these results suggest that the observed reduction in hepatic vector DNA levels in juvenile mice is attributable to vector $(b) (4)$ due to ongoing hepatic growth.*

Study #10 (Study DTX401-22-0009)

A 3-month single dose toxicity study of DTX401 by intravenous injection in mice

- 9-week-old male and female wildtype mice were IV administered either 6×10^{13} gc/kg DTX401 or vehicle control on Day 1 (n=10/sex/timepoint). Mice were sacrificed on Day 8, Day 29, or Day 92 for evaluation of vector distribution in blood, semen, liver, epididymis, and salivary glands. Vector distribution in blood, urine, and feces was evaluated beginning on Day 2 through Day 92.
- Vector DNA was detected in liver, epididymis, and salivary glands in DTX401-administered animals at all timepoints. Vector DNA was detected in all bodily fluids peaking at the earliest timepoint. By Day 92, vector DNA was either below the level of quantification or below the level of detection (BLOD) in all blood samples. Vector DNA was BLOD in all samples by Day 64, Day 29, Day 8, and Day 92 for urine, feces, saliva, and semen, respectively.

Reviewer Comments:

- *This study supports the resolution of vector shedding following IV administration of DTX401 within the duration of this 92-day study.*

Study #11

Report Number		DTX401-22-0006
Date Report Signed		15-NOV-2023
Title		A 6 Month Single Dose Intravenous Pharmacology and Toxicology Study of DTX401 in Cynomolgus Monkeys
GLP Status		Yes
Testing Facility		(b) (4)
Objective(s)		To evaluate potential toxicity of IV DTX401 administration in NHPs with a 6-month recovery period.
Study Animals	Strain/Breed	(b) (4)
	Species	(b) (4)
	Age	2.4-2.9 years (juvenile)
	Body Weight	Males: 1.9-2.7 kg Females: 1.8-2.3 kg
	#/sex/group	3/sex/group
	Total #	18
Test Article		DTX401 (lot # D401-500P-W22-02)
Control Article		Vehicle (Same as Study # 8)
Route of Administration		IV
Description of the Administration Procedure		Test or control article was administered as a single IV bolus on Day 1.
Study Groups and Dose Levels		Group 1 – Vehicle Group 2 – DTX401 1.0×10^{13} gc/kg Group 3 – DTX401 7.0×10^{13} gc/kg
Dosing Regimen		Single administration
Randomization		Yes
Description of Masking		Not described
Scheduled Sacrifice Time Points		Day 183

Key Evaluations and Assessments:

- Animals were monitored twice daily for morbidity/mortality. Detailed clinical observations and body weight monitoring were performed weekly beginning at least one week prior to Day 1.
- Neurological examinations, body temperature, blood pressure and heart rate were conducted pre-dose, and 1- and 24- hours post-dose. Jacketed external telemetry (electrocardiography) was evaluated pre-dose, for a 24-hour period on Day 1. Respiration rates and pulse oximetry were evaluated pre-dose, 1-2 hours post-dose, and 24 hours post-dose. All safety pharmacology evaluations were also repeated near the end of Months 3 and 6.
- Blood and urine samples were collected for hematology, coagulation, clinical chemistry, and urinalysis once pre-dose and on Days 8, 29, 92, and 182. Blood for cytokine evaluation was collected once pre-dose, 4- and 24-hours post-dose, and on Days 84 and 182. Blood for total Ab evaluation was collected pre-dose, and on Days 7, 14, 84, and 182. Blood samples for BD were collected on Days 4, 5, 15, 16, 29, 30, 57, 58, 92, 93, 141, 142, 182, and 183. Vector DNA was evaluated at all timepoints; vector mRNA was only evaluated on alternate days.
- A full list of tissues were collected at necropsy for histopathology analysis. Additional liver tissue was collected for BD analysis.

Key Results:

- All NHPs survived to their scheduled necropsy time point.
- Minimal ALT elevations were noted in one male in the 7.0×10^{13} gc/kg group on Day 8 ($1.91 \times$ baseline) and Day 92 ($1.63 \times$ baseline) as well as in the female 7.0×10^{13} gc/kg group on Day 92 ($2.04 \times$ group baseline mean). No differences were noted on Day 183.
- Anti-AAV8 Abs were detected in a total of 8 of the 18 NHPs in this study 2 weeks prior to DTX-401 or vehicle administration. Elevations in anti-AAV8 Abs were detected in all NHPs administered DTX401 from Day 7 through the end of the study, peaking around the Day 84 and Day 182 timepoints.
- Vector DNA levels in the blood and liver were dose-dependent, peaked at the earliest timepoint (4 hours post-administration), and decreased thereafter. Vector RNA was only detected sporadically in blood samples. In Day 183 liver samples, vector DNA and RNA were detected at 4.9×10^6 copies/ μ g DNA and 5.5×10^3 copies/ μ g RNA for the 1.0×10^{13} gc/kg group. This finding was dose dependent, as vector DNA and transgene RNA levels were $4.5 \times$ and $13.3 \times$ higher respectively in the 1.0×10^{13} gc/kg group at the same timepoint. Vector DNA and RNA were not detected in NHPs administered vehicle.

Reviewer Comment:

- *This study supports the safety of a single IV administration of DTX401 in healthy juvenile NHPs at dose levels up to 7.0×10^{13} gc/kg. This dose level is equivalent to $(b) (4) \times 10^{14}$ gc/kg using the final (b) (4) method for titer determination.*

Study #12

Report Number		DTX401-23-0004
Date Report Signed		13-NOV-2024
Title		An embryo-fetal development study of DTX401 by intravenous injection in mice
GLP Status		Yes
Testing Facility		(b) (4)
Objective(s)		To evaluate the effect of DTX01 administration on pregnant C57BL/6 female mice and development of the embryo and fetus following dam exposure.
Study Animals	Strain/Breed	C57BL/6 mice
	Species	(b) (4)
	Age	85 days old
	Body Weight	19.6 – 26.0 g
	#/group	18 pregnant dams/group
Total #		54 dams
Test Article		DTX401 (lot: D401-500P-C24-01)
Control Article		DTX401 vehicle (20 mM Tris, (b) (4) Magnesium Chloride (b) (4), 0.01% w/v Poloxamer 188, 200 mM Sodium Chloride in Sterile water, pH (b) (4)
Route of Administration		IV
Description of the Administration Procedure		Naïve male and female C57BL/6 mice were cohabited for up to 5 days.

	A total of 87 presumed pregnant female mice were randomly assigned to three groups (n=29/group) and administered 5 mL/kg of either test or control article as a bolus IV injection on presumed GD 6. Excess mice were administered to achieve a minimum of 54 pregnant mice (18 dams/group).
Study Groups and Dose Levels	Group 1 – Vehicle control Group 2 – DTX401, 1×10^{13} gc/kg Group 3 – DTX401, 7×10^{13} gc/kg
Dosing Regimen	Single administration
Scheduled Sacrifice Time Points	GD 18

Key Assessments:

- Morbidity and mortality were evaluated twice a day.
- Detailed clinical observations were conducted on GD 6 (pre-dose), and on GDs 9, 12, 15, 16, and 18.
- Cageside observations were conducted weekly during acclimation, 1-, 4-, and 24-hours following administration, and daily thereafter.
- Maternal body weights were measured weekly during acclimation and on GDs 6, 9, 12, 15, 16, and 18.
- Vector BD in the blood was evaluated in 5 mice per group on GDs 9 and 18.
- Terminal evaluations of the dams consisted of gross necropsy, ovarian and uterine examination, body weight and gravid uterus weight. Fetal evaluations included visceral and skeletal abnormalities.
- BD was evaluated in the liver and placenta of dams (5 animals per group) and in the liver of one male and one female fetus per dam.

Key Results:

- All dams survived to the assigned terminal endpoint (GD 18, 12 days post-administration). There were no DTX401-related findings in clinical signs, body weight, or terminal evaluations of dams.
- There were no DTX40-related fetal abnormalities. A total of 138-151 fetuses per study group were evaluated.
- DTX401 DNA was detected in all whole blood samples from Group 2 and Group 3 dams and in a single Group 1 sample (GD 9, 643 copies/ μ g DNA). Detection was dose-dependent and peaked on GD 9 at 2.0×10^6 and 2.4×10^7 copies/ μ g DNA in Groups 2 and 3, respectively. On GD 18, DTX401 was detected in blood at 3.6×10^5 and 8.9×10^5 copies/ μ g DNA in Groups 2 and 3, respectively.
- DTX401 DNA levels were dose-dependent and detected in liver and placenta samples from all dams on GD 18. BD in the liver was 2.3×10^6 and 1.9×10^7 copies/ μ g DNA in Groups 2 and 3, respectively. BD in the placenta was 1.2×10^4 and 5.0×10^5 copies/ μ g DNA in Groups 2 and 3, respectively.
- DTX401 DNA was not detected in any fetal liver samples from any group, or in any tissue samples from vehicle-administered mice.

Reviewer Comments:

- *There were no findings of embryo-fetal toxicities observed in this study.*

- This study supports a NOAEL of 7.0×10^{13} gc/kg for maternal and fetal toxicity. This is equivalent to (b) (4) $\times 10^{14}$ gc/kg using the final (b) (4) method for titer determination.

Study #13

Report Number		DTX401-23-0006
Date Report Signed		27-MAY-2025
Title		A germline transmission study in offspring of mice following a single intravenous dose of DTX401 in mice
GLP Status		Yes Exceptions: liver integration analysis
Testing Facility		(b) (4)
Objective(s)		To assess germline transmission following DTX401 administration.
Study Animals	Strain/Breed	C57BL/6 mice
	Species	(b) (4)
	Age	Males: 15 weeks old Females: 11 weeks old
	Body Weight	Males: 25.4 – 32.7 g Females: 17.9 – 23.3 g
	#/group	30/sex/group
	Total #	180
Test Article		DTX401 (lot: D401-500P-W23-02)
Control Article		DTX401 vehicle (20 mM Tris, (b) (4) Magnesium Chloride (b) (4), 0.01% w/v Poloxamer 188, 200 mM Sodium Chloride in Sterile water, pH (b) (4)
Route of Administration		IV
Description of the Administration Procedure		On Day 1 of the study, male and female C57BL/6 mice were administered a bolus IV injection of 5 mL/kg of either vehicle or test article. 37 days later, male and female mice were cohabitated at a 1:1 ratio with either confirmed C57BL/6 male breeders (Groups 1-2), or C57BL/6 females (Groups 3-4). Mice were cohabitated for a maximum of 7 days.
Study Groups and Dose Levels		Female mice mated with untreated males: Group 1 – Vehicle control Group 2 – DTX401, 7×10^{13} gc/kg Male mice mated with untreated females: Group 3 – Vehicle control Group 4 – DTX401, 7×10^{13} gc/kg
Dosing Regimen		Single administration
Scheduled Sacrifice Time Points		F ₀ male mice: Day 48 $\pm$ 2 F ₀ dams: Days 15 through 21 postpartum F ₀ dams that did not deliver: GD 23 F ₀ dams with no surviving pups: On the day the observation is made F ₁ mice: PNDs 15 through 21

Key Assessments:

F₀ generation:

- Mortality- Twice daily
- Cage-side observations: 1-, 4-, and 24-hours post-administration, daily thereafter

- Body weight and clinical observations: Weekly beginning on Day 1
- Mating and fertility: Mating index, fertility index, and pregnancy index
- Natural delivery and litter observations
- (b) (4) vector DNA: Terminal blood, liver, ovaries, and testes
- Gross necropsy, ovarian and uterine examinations

F₁ generation:

- Mortality: Twice daily.
- Clinical observations, body weight: PNDs 2, 4, 7, 10, 14, and/or 21.
- (b) (4) vector DNA: Terminal blood (pooled) and livers from offspring of DTX401-administered mice. Blood from male and female mice were pooled separately.
- Target enrichment sequencing integration site analysis of liver samples: 3 pups/sex/litter from the first 15 successful pregnancies (Groups 2 and 4) or 1 pup/sex/litter from the first 5 successful pregnancies (Groups 1 and 3).
- Gross necropsy

Key Results:

F₀ generation:

- No deaths were attributed to DTX401 administration in this study.
 - All male mice survived to scheduled euthanasia.
 - One vehicle female was found dead on Day 17, one DTX401 female was euthanized on Day 10 due to an eye rupture, and two DTX401 females were euthanized due to a lack of surviving pups, per study protocol.
- No DTX401-related effects were noted in clinical observations, body weights, or reproductive indices in male or female mice. A statistically significant decrease in implantation sites in DTX401-administered males compared to vehicle (10.5 vs 8.7 sites per mouse, $p \leq 0.05$, Dunn's test) was not attributed to DTX401, as it was driven by only 2 DTX401-administered animals.
- There were no DTX401-related abnormalities noted as part of macroscopic pathology or ovarian and uterine examinations.
- BD:
 - All samples from vehicle-administered mice were negative for DTX401.
 - DTX401-administered females: DTX401 DNA was detected in dam livers (2.70×10^6 copies/ μ g DNA) and ovaries (7.98×10^4 copies/ μ g DNA), but not in terminal blood samples.
 - DTX401-administered males: DTX401 was detected in male livers (2.64×10^6 copies/ μ g DNA), testes (1.23×10^5), and blood (1.72×10^5) collected on Day 48.

F₁ generation:

- DTX401 administration in F₀ mice had no observable effect on in-life evaluations of F₁ mice. Adverse clinical findings were limited to individual litters and were common findings for perinatal mice.
- DTX401 DNA was not detected in any liver or pooled blood sample collected from F₁ mice.

- The level of genomic integration in the liver was not significantly different between samples from F₁ mice that were offspring of vehicle or DTX401-administered F₀ mice, indicating a lack of integration.

Reviewer Comments:

- *This study supports a NOAEL of 7.0×10^{13} gc/kg for maternal and fetal toxicity. This is equivalent to (b) (4) $\times 10^{14}$ gc/kg using the final (b) (4) method for titer determination.*
- *These results are consistent with a lack of integration in germline cells in the F₀ generation, as there was no vector detection in the F₁ offspring.*

APPLICANT'S PROPOSED LABEL

Section 5.3 'Malignancy' was revised to accurately reflect the available nonclinical data.

Section 8.1 'Pregnancy' was revised to accurately reflect the available nonclinical data.

Section Section 8.3 'Females and Males of Reproductive Potential' was revised to accurately reflect the available nonclinical data.

Section 12.1 'Mechanism of Action' was revised to accurately reflect the available nonclinical data.

Section 12.2 'Pharmacodynamics' was revised to accurately reflect the available nonclinical data.

Section 13 'Nonclinical Toxicology' was revised to accurately reflect the available nonclinical data.

CONCLUSION OF NONCLINICAL STUDIES

Review of the nonclinical studies did not identify any safety concerns that could not be adequately addressed in labeling. The nonclinical data support approval of the biologics license application.

KEY WORDS/TERMS

AAV, AAV8, cynomolgus macaque, DTX401, gene therapy, GENGLYCOS™, glucose, glycogen storage disease type Ia, G6Pase, GSDIa, inborn error of metabolism, mouse model, nonhuman primate, pariglasene brecaparvovec-opnr, von Gierke disease

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