

Volixibat safety data support first clinical trial of IBAT inhibitors in intrahepatic cholestasis of pregnancy



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Introduction

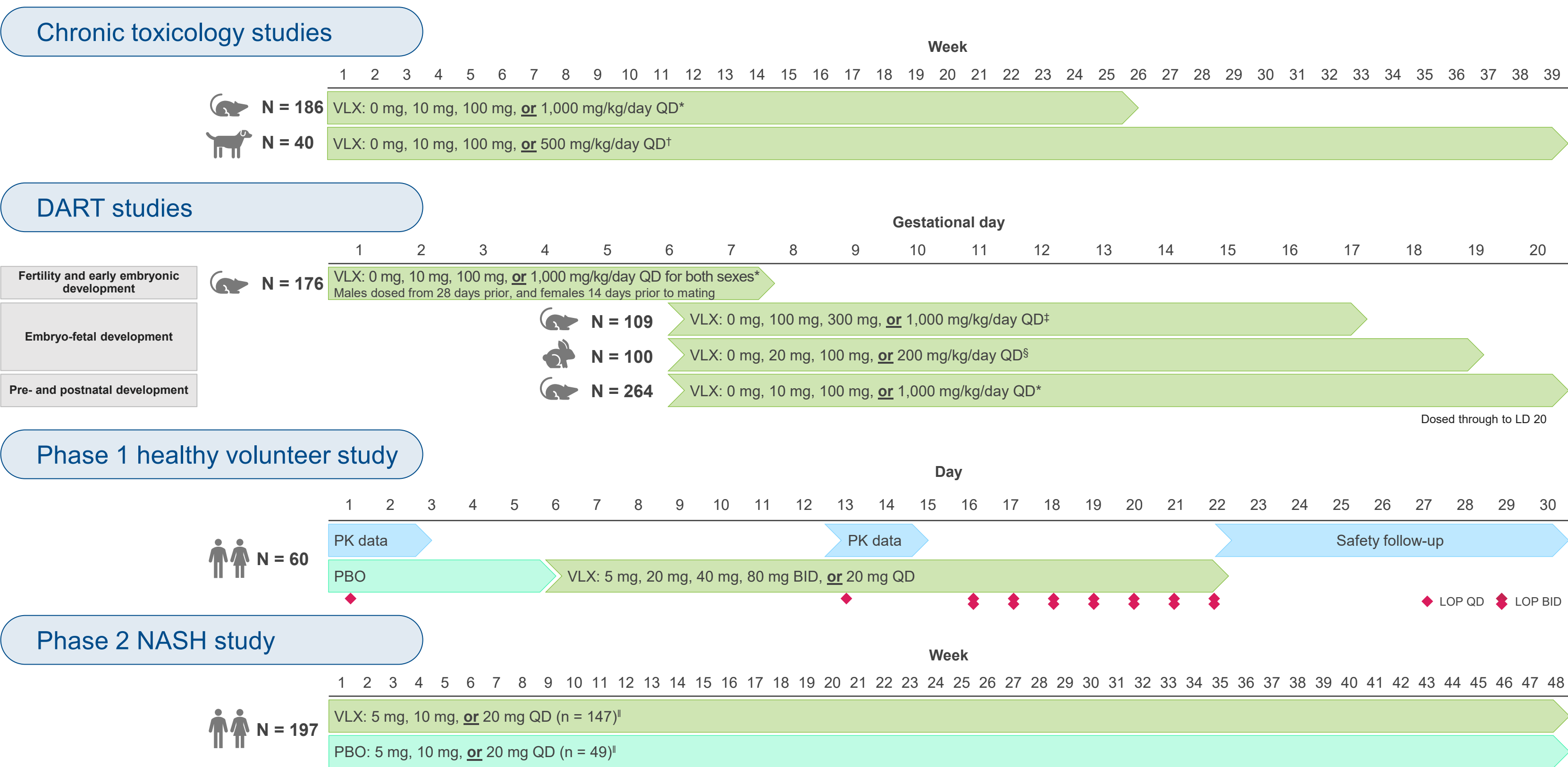
- Intrahepatic cholestasis of pregnancy (ICP), the most common pregnancy-specific liver disease, is characterized by maternal pruritus and increased serum bile acids (sBAs).¹
- Elevated sBAs in ICP are correlated with maternal morbidity and poor fetal outcomes, including increased risk of preterm delivery, intrapartum fetal distress, and stillbirth.²⁻⁴
- Off-label therapies, including ursodeoxycholic acid, remain suboptimal and offer limited or no effectiveness in reducing pruritus or improving perinatal outcomes in ICP.^{5,6}
- Volixibat (VLX) is a minimally absorbed ileal bile acid transporter inhibitor (IBATi) that has been dosed in over 400 clinical trial participants.⁷
- VLX interrupts the enterohepatic recirculation of bile acids, thus reducing sBAs and potentially improving cholestasis, pruritus, and fetal outcomes in ICP.^{7,8}

Design

- Non-clinical chronic toxicology and developmental and reproductive toxicology (DART) studies, and safety and pharmacokinetic data from human clinical trials were reviewed to assess VLX's suitability in patients with ICP.

Methods

Figure 1. Dosing schedule and endpoints for the chronic toxicology studies, DART studies and human clinical trials.



Study	Species	Key endpoints
Chronic toxicology	Rat, Beagle dog	All general toxicology readouts
DART studies		
Fertility and early embryonic development	Rat	Male and female fertility measures and early fetal health
Embryo-fetal development	Rat, rabbit	Embryonic and fetal health
Pre- and postnatal development	Rat	Embryonic and fetal health, postnatal health including lactation, success of offspring through sexual maturity
Human clinical trials		
Healthy volunteer study	Human	Safety, PK, and PD in healthy volunteers
NASH study	Human	Safety, PK, and PD in patients with NASH

*Dosed by oral gavage to adult Sprague Dawley rats; †Dosed by oral gavage to adult Beagle dogs; ‡Dosed by oral gavage to adult albino and Sprague Dawley-derived rats; §Dosed by oral gavage to adult rabbits; ¶Adult participants received VLX or PBO in a blinded fashion. BID, twice-daily; DART, developmental and reproductive toxicology; LD, lactation day; LOP, loperamide; NASH, non-alcoholic steatohepatitis; PBO, placebo; PD, pharmacodynamics; PK, pharmacokinetics; QD, once-daily; VLX, volixibat.

Results

Safety and tolerability

Chronic toxicology studies

- No adverse effects were observed up to the highest doses tested (rat: NOAEL ≥1,000 mg/kg/day, 70-fold safety margin; dogs: NOAEL ≥500 mg/kg/day, 120-fold safety margin).
- VLX also did not demonstrate any *in vivo* or *in vitro* genotoxicity across four separate test systems: Ames mutation assay, mouse lymphoma cell mutation assay, human peripheral blood lymphocyte chromosomal aberration assay, or rat bone marrow micronucleus *in vivo* assay.

Table 1. VLX had no adverse effect on any endpoints studied in chronic toxicology studies.

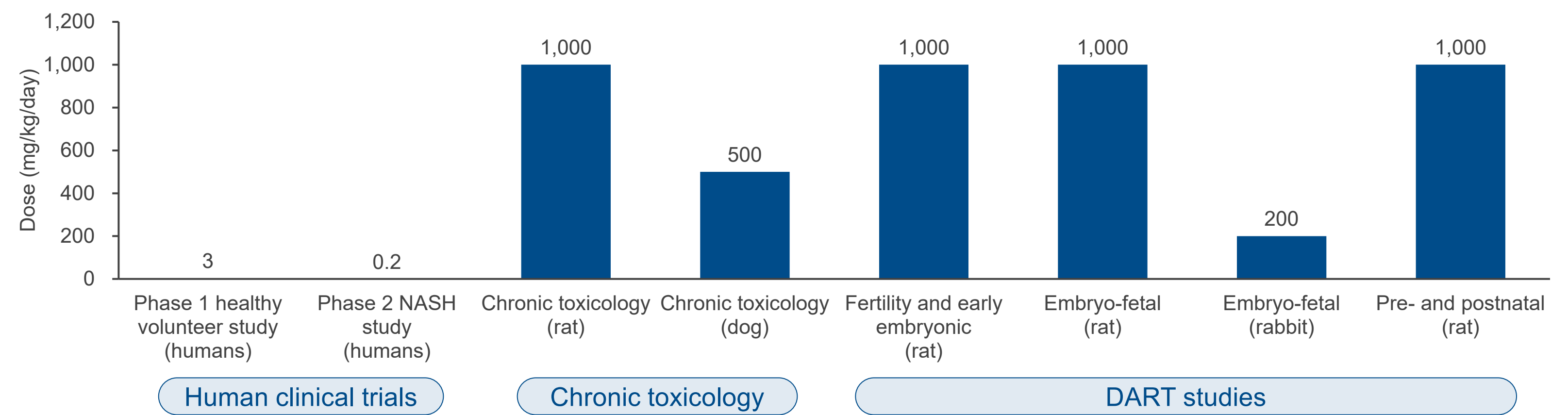
✓ = no adverse effect	Rat	Dog
Clinical observations	✓	✓
Ophthalmoscopic exam	✓	✓
Body weights	✓	✓
Food consumption	✓	✓
Clinical pathology	✓	✓
Red blood cell parameters	✓	✓
Differential leukocyte counts	✓	✓
Coagulation measurements	✓	✓
Liver function parameters	✓	✓
Kidney function parameters	✓	✓
Serum electrolytes	✓	✓
Urinalysis and chemistry	✓	✓
Tissue examination at necropsy	✓	✓
Organ weights	✓	✓
Histopathology of GLP list of tissues	✓	✓
Peripheral blood and bone marrow smears	✓	✓

VLX, volixibat.

Volixibat pharmacokinetics

- In human clinical trials, VLX was minimally absorbed with very low or undetectable plasma drug concentrations below the lower limit of quantification (0.05 ng/mL).
- Large clinical safety margins, from 28- to 120-fold, were established in rat, rabbit, and dog toxicology studies (**Figure 2**).

Figure 2. High doses tested in the human clinical trials, chronic toxicology, and DART studies to establish large safety margins to clinical doses.



DART, developmental and reproductive toxicology; NASH, non-alcoholic steatohepatitis.

DART studies

- Fertility and early embryonic development study: VLX had no effect on clinical findings or reproductive and fertility outcomes at any dose levels evaluated.
- Embryo-fetal development studies: VLX had no adverse effects on fetal development at any dose level.
- Pre- and postnatal development study: no adverse effects in pre- and postnatal development were noted after VLX administration (**Table 2**).
- The no-observed-adverse-effect levels were greater than or equal to the highest doses tested in each case, with safety margins of 28- to 70-fold across the studies.

Table 2. VLX had no adverse effect on any endpoints evaluated in the DART studies.

✓ = no adverse effect	Fertility and early embryonic (rat)	Embryo-fetal (rat)	Embryo-fetal (rabbit)	Pre- and postnatal (rat)
Clinical observations	✓	✓	✓	✓
Body weights	✓	✓	✓	✓
Food consumption	✓	✓	✓	✓
Fertility function	✓	N/A	N/A	✓*
Reproductive organ function	✓	N/A	N/A	✓*
Litter size	✓	✓	✓	✓
Placental exam	✓	✓	✓	✓
Fetal weights	N/A	✓	✓	✓
Fetal external exam	N/A	✓	✓	✓
Fetal visceral exam	N/A	✓	✓	✓
Fetal skeletal exam	N/A	✓	✓	✓
Clinical observation of pups	N/A	N/A	N/A	✓
Pup weight gain	N/A	N/A	N/A	✓
Lactation and weaning	N/A	N/A	N/A	✓
Pup developmental milestones	N/A	N/A	N/A	✓
Pup reproductive function	N/A	N/A	N/A	✓

*Mature pups. DART, developmental and reproductive toxicology; N/A, not applicable; VLX, volixibat.

Phase 1 healthy volunteer study (N = 60)

- Safety outcomes were similar across all dose cohorts, with only mild (grade 1)-to-moderate (grade 2) treatment-emergent adverse events (TEAEs).
- No serious TEAEs were reported.
- Gastrointestinal (GI) disorders were the most commonly reported TEAEs; the majority of cases being grade 1, and no dose-dependent differences were noted.
 - The majority of diarrhea events resolved prior to or with administration of loperamide.
- One participant with a past medical history of hematochezia reported a grade 2 AE of hematochezia, which was deemed related to VLX.

Phase 2 NASH study (N = 197)

- TEAEs leading to treatment discontinuation were reported in 11% of patients treated with VLX (majority [8%] due to GI-related events).
- TEAEs were mostly GI-related and were mild to moderate in severity, transient, and self-limiting.

Conclusions

- ICP is the most common pregnancy-specific liver disease, and available therapies (off-label, including ursodeoxycholic acid) offer limited or no effectiveness in reducing pruritus or improving perinatal outcomes.^{1,5,6}
- VLX is a minimally absorbed IBATi that has been administered to over 400 clinical trial participants; it increases fecal excretion of bile acids, and is generally well tolerated across Phase 1 and Phase 2 clinical trials.
- No safety risks were identified in the VLX chronic toxicology or DART investigations, establishing safety margins of at least 28-fold and up to 120-fold, predicting that VLX will likely be safe in the setting of pregnancy.

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