4793: Lack of Reproductive and Developmental Toxicity for AT-527 (Bemnifosbuvir), an Oral Purine Nucleotide Prodrug for COVID-19 Infection

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Introduction

AT-527 (bemnifosbuvir), the hemisulfate salt of AT-511 (free base), is an orally administered double prodrug of a guanosine nucleotide analog that is converted after multi-step activation to the active 5′-triphosphate (TP) metabolite (AT-9010). AT-9010 inhibits the replication of COVID-19 viruses through a dual mechanism of action targeting both NiRAN and RdRp domains (Shannon et al. 2022). It has demonstrated potent anti-COVID-19 activity in vitro (EC_{90}=0.5 μM) and exhibited a well-tolerated safety profile in patients. Here we report the potential effects of AT-527 on the reproductive and developmental function. The general nonclinical toxicity profile of AT-527 is presented in P#858.

Materials and Methods

AT-527 was supplied by Atea Pharmaceuticals, Inc. and formulated in PEG-400 (40%, v/v) / Solutol HS15 (10%, v/v)/ 100 mM Citrate buffer pH 4.5±0.2 (50%, v/v). The dose levels were expressed as free base (AT-511)-equivalent.

Crl:CD(SD) Sprague Dawley rats were obtained from Charles River Laboratories, Raleigh, NC. Female New Zealand White [Crl:KBL(NZW)] rabbits were obtained from Charles River Laboratories, Saint Constant, Quebec, Canada. All animal studies were conducted in a facility fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC). All procedures were performed in accordance with the Guide for the Care and Use of Laboratory Animals and Animal Welfare and approved by the local Institutional Animal Care and Use Committee (IACUC). All definitive studies were conducted in compliance with GLP regulations.

One-way analysis of variance (ANOVA) and pairwise comparisons (Dunnett's test) were performed. Statistical significance was reported at the probability levels of 0.05 and 0.01.

Results

A standard DART program was conducted to characterize the potential effects of AT-527 on the developmental and reproductive functions as shown in Table 1.

Table 1: Reproductive and Developmental Toxicity Studies with AT-527 in Rats and Rabbits

Study Type	Summary of Results
Seg I, Fertility and early embryo-fetal development study in rats	• 0, 250, 500 and 1000 mkd; 22/sex/group • ↑incidence of abnormal breathing sounds at 500 and 1000 mkd • ↓body weights (ca 4% to 13% Days 36 to 58) and body weight gains (ca 10% Days 1 to 57) in males at 1000 mkd • NOAEL: 1000 mkd
Seg II, DRF Embryo-fetal development study in rats	• 0, 250, 500 and 1000 mkd, GD 7 to 17, Tox: 6 ♀/group; TK: 9 ♀/group for dosed groups • No findings at doses up to 1000 mkd
Seg II, Definitive Embryo-fetal development study in rats	• 0, 250, 500 and 1000 mkd, GD 7 to 17, Tox: 22 ♀/group; TK: 9 ♀/group except for 3 females for control • NOAEL: 1000 mkd for maternal and developmental toxicities
Seg II, DRF Embryo-fetal development study in rabbits	• 0, 125, 250, 500 mkd, GD 7 to 19, 6 ♀/group • At 125 mkd: apparent reductions of FC, minimal maternal BW loss, slightly lower fetal body weight • ≥ 250 mkd: mortalities with markedly ↓FC, BW loss and clinical observations
Seg II, Definitive Embryo-fetal development study in rabbits	• 0, 25, 50, 100 mkd, dosing on GD 7 to 19, 22 ♀/group • ≥ 25 mkd: ↓maternal FC and BW gain • At 100 mkd: abortions and mortality (Table 2) with ↓FC (Table 3) and BW loss during dosing period (GD7-19) (Figure 1) • NOAEL: 100 mkd for developmental toxicity
Seg III, Pre- and postnatal development study in rats with behavioral/functional evaluation	• 0, 250, 500 and 1000 mkd, dosing on GD 7 to LD 20, 22 ♀/group • NOAEL: 1000 mkd for maternal and developmental toxicities

mkd = mg/kg/day, FC = food consumption, BW = body weight, GD = gestation day, LD = lactation day, ♀ = female

Table 2: Summary of Mortality and Abortions in the Definitive Seg II Study in Rabbits

Mode of Death	Dose (mkd)			
	Vehicle	25	50	100
Abortion	NA	1/22	1/22	3/22
Unscheduled Sacrifice	NA	NA	NA	1/22
Total	**0/22**	**1/22**	**1/22**	**4/22**

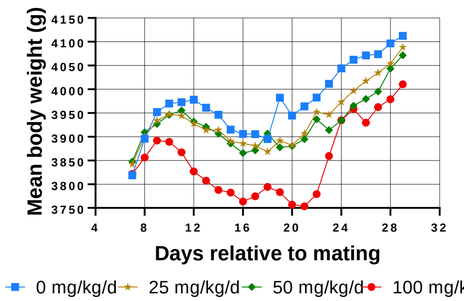
mkd = mg/kg/day, NA = not applicable

Table 3: Summary of Food Consumption (g/day) in the Definitive Seg II Study in Rabbits

Interval		Dose (mkd)			
		Vehicle	25	50	100
GD7-20	M ± SD	102 ± 36	89 ± 39	85 ± 34	71 ± 31
	Change	NA	↓13%	↓17%	↓37%
GD20-29	M ± SD	115 ± 30	111 ± 29	118 ± 32	128 ± 29
	Change	NA	↓3%	↑3%	↑11%
GD7-29	M ± SD	108 ± 27	98 ± 26	100 ± 28	97 ± 29
	Change	NA	↓9%	↓8%	↓10%

mkd = mg/kg/day, GD = gestation day, M = mean, SD = standard deviation, NA = not applicable

Figure 1: Summary of Mean Body Weight in the Definitive Seg II Study in Rabbits



Conclusions

- There were no AT-527-related effects on the fertility, reproduction, embryofetal and postnatal development in rats. The NOAEL was 1000 mg/kg/day, the top dose tested, in Segment I, II and III studies.
- In rabbits, there were no AT-527-related embryofetal abnormalities at doses up to 100 mg/kg/day even in the presence of evident maternal toxicities at 100 mg/kg/day, i.e., body weight loss, abortions, and mortalities, which were secondary to reduced food consumption.
- The maternal toxicity of AT-527 in rabbits was confounded by the toxicity caused by the vehicle as the PEG-400-containing complex vehicle itself resulted in reduced food consumption and body weight loss noted in a 7-day tolerability study in nonpregnant female rabbits.

References

1. *Shannon A, Fattorini V, SamaB, et al.. A dual mechanism of action of AT-527 against SARS-CoV-2 polymerase. Nature Communications 2022, 13:621.*

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