

# Etravirine has no effect on fetal development in rats and rabbits

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# Abstract

#### Background

The effect of etravirine (ETR: TMC125) on embryo-fetal and pre and postnatal development was assessed in pregnant rats and rabbits

## Methods

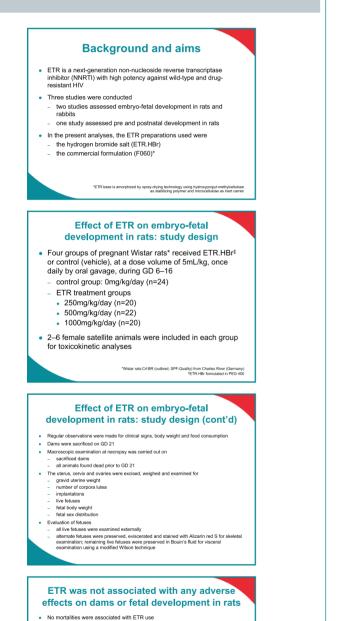
In the embryo-fetal study, ETR was administered at several oral doses up to 1000mg/kg/day in rats and 375mg/kg/day in rabbits during the period of fetal organogenesis (Gestation Day [GD] 6 to Day 16 in rats and Day 19 in rabbits). The uterus was examined and the number of implantations, live fetuses, fetal weight and sex distribution were analyzed. Fetuses were subject to external and visceral examination. In the pre and postnatal study, ETR was administered (up to 500mg/kg/day) to pregnant rats from Day 7 of gestation through Day 21 of lactation. The clinical conditions, sensory functions, and behavior and reproductive performance of the first generation were assessed.

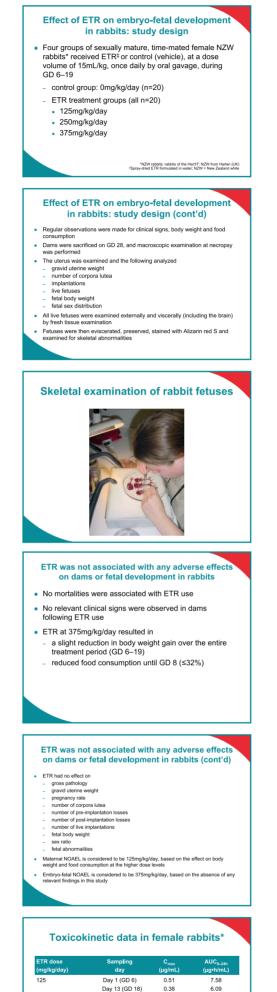
### Results

ETR showed no adverse effect on embryo-fetal development at any doses tested in rats or rabbits. ETR also had no effect on offspring development and maturation during lactation or postweaning in rats. In these studies, maternal systemic exposure to ETR was equivalent to the clinical exposure (area under the plasma concentration-time curve from time of administration to 24 hours after dosing; AUC<sub>a au</sub>=7.4µg•h/mL) at the recommended therapeutic dose (200mg twice daily) at the end of treatment and was 2-3-fold higher at the beginning of dosing during the early stages of organogenesis

#### Conclusions

These studies confirm that ETR was safe in pregnant rats and rabbits.





	vations were made for maternal clinical wed to litter, and nesting and nursing b		nd food consumption
<ul> <li>Clinical observa</li> </ul>	r size and numbers of each sex were re ations in pups and pup body weight wer	re recorded	
<ul> <li>Developmental</li> <li>ears open</li> <li>eyes open</li> </ul>	landmarks were recorded for offspring;	; the number with	
<ul> <li>preputial se</li> <li>vagina ope</li> <li>Sensory function</li> </ul>	an		
<ul> <li>static righti</li> <li>startle resp</li> </ul>	ponse		
<ul> <li>pupillary lig</li> <li>tail flick tes</li> </ul>			
<ul> <li>reproductiv</li> </ul>	ve performance learning, memory and locomotor activity	1)	
Effect o	f ETR on maternal a	and pre and	t nostnatal
	lopment in rats: stu		
	ere sacrificed at litter we scopic evaluation was		
female	es, including counting th		
<ul> <li>a rang</li> </ul>	in each uterine horn je of tissue and organ s		e preserved,
	et examined microscopi		formed
<ul> <li>a rang</li> </ul>	opic evaluation of offsp je of tissue and organ s	samples wer	
but no	t examined microscopi	cally	
	use had no effect		
	and postnatal dev		in rats
<ul> <li>No relevant</li> </ul>	es were associated with ETR L clinical signs or effects on bod observed following ETR use		consumption of
<ul> <li>Maternal tre</li> </ul>	eatment with ETR had no effect	t on	
<ul> <li>gestation</li> <li>parturition</li> </ul>	on		
<ul> <li>sex ratio</li> </ul>			
<ul> <li>pup surv</li> <li>clinical c</li> </ul>	condition	Incoded output 1	then in control
<ul> <li>no clear</li> </ul>	t was higher in pups from ETR dose response was observed		
	dition, sensory function/reflexe e of offspring were unaffected		
	use had no effect		
	postnatal develop		
	nce for an effect of ETR u or offspring	use on macros	scopic findings
	NOAEL is considered to ace of any effect in this st		'day, based or
<ul> <li>no dela</li> </ul>	ayed effects of maternal t ed for development to adu	treatment on o	
physica	al development, sensory or, sexual maturation or r	functions, ref	exes,
<ul> <li>The NOAI</li> </ul>	EL for pup development	following mate	ernal treatmen
	is considered to be 500m of any effect in this study		sed on the
Τοχία	cokinetic data	in fema	le rats*
	Sampling	C <sub>max</sub>	AUC‡
ETR dose	day	(μg/mL) 1.03	(µg∙h/mL) 6.15
ETR dose (mg/kg/day) 125			
(mg/kg/day) 125	Day 1 (GD 7) Day 11 (GD 17)	0.65	5.29
(mg/kg/day)	Day 1 (GD 7)	0.65 1.30 0.85	9.42 7.60
(mg/kg/day) 125	Day 1 (GD 7) Day 11 (GD 17) Day 1 (GD 7)	1.30	9.42
(mg/kg/day) 125 250 500 • Exposures in therapeutic	Day 1 (GD 7) Day 11 (GD 17) Day 1 (GD 7) Day 11 (GD 17) Day 11 (GD 7)	1.30 0.85 1.66 0.64	9.42 7.60 12.10 3.63 recommended
(mg/kg/day) 125 250 500 • Exposures in	Day 1 (GD 7) Day 11 (GD 17) Day 11 (GD 17) Day 11 (GD 17) Day 11 (GD 17) Day 11 (GD 7) Day 11 (GD 17) in rats are equivalent to those i	1.30 0.85 1.66 0.64 in patients at the and AUC <sub>0-24h</sub> 7.4	9.42 7.60 12.10 3.63 recommended 4µg•h/mL at

• ETR use was not associated with adverse effects on embryo-fetal development in:

- gross pationary where observed = ETR had no effect on gravid uterine weight number of corpora lutea number of pre-implantation loss number of post-implantation los number of pive implantations

- fetal body weight
- fetal abnormalities
- The maternal and embryo-fetal NOAEL is considered to be 1000mg/kg/day based on the absence of any effect

No relevant clinical signs, or effects on body weight and food consumption, or on gross pathology were observed

NOAEL = No Observed Adverse Effect Level

### Toxicokinetic data in female rats\*

Toxicokinetic analysis indicated nonlinear pharmacokinetic

ETR dose (mg/kg/day)	Sampling day	C <sub>max</sub> (μg/mL)	AUC <sub>0–24h</sub> (µg∙h/mL)			
250	Day 11 (GD 16)	0.51	3.26			
500	Day 11 (GD 16)	0.58	7.94			
1000	Day 11 (GD 16)	0.57	8.27			
• Exposures in rats are equivalent to those in patients at the recommended therapeutic dose (human $C_{max}$ 0.45µg/mL and AUC_{0-24h} 7.4µg•h/mL at 200mg bid)						
	$^*C_{\rm max}$ and ${\rm AUC}_{\rm 3-24h}$ value		oral administration, GD 6-16 ximum plasma concentration			

250	Day 1 (GD 6) Day 13 (GD 18)	0.63 0.41	11.6 5.27	
375	Day 1 (GD 6) Day 13 (GD 18)	0.70 0.54	12.3 9.67	

Exposures in rabbits are equivalent to those in patients at the recomme therapeutic dose (human  $C_{\rm max}$  0.45µg/mL and AUC\_{0-24h} 7.4µg-h/mL at 200mg bid)

\*C<sub>max</sub> and AUC<sub>D-240</sub> values of spray-dried ETR after repeated oral adm

#### Effect of ETR on maternal and pre and postnata development in rats: study design

- Four groups of time-mated female Sprague-Dawley rats\* received ETR\* or control (vehicle), at a dose volume of 20mL/kg, once daily by oral gavage, during GD 7 to Day 21 of lactation
- control group: 0mg/kg/day (n=28)
- ETR treatment groups (all n=28)
- 125mg/kg/day
- 250mg/kg/da
- 500mg/kg/day
- offspring (first generation pups) were allowed to mature untreated
- Six time-mated female satellite animals were included in each group for toxicokinetic analyses

\*Sprague-Dawley:CrI:CD BR from Charles River (UK) \*Spray-dried ETR formulated in water

- pregnant Wistar rats at levels up to 1000mg/kg/day
- pregnant NZW rabbits at levels up to 375mg/kg/day.
- In both species, maternal exposure at the end of treatment was equivalent to human exposure at the recommended therapeutic dose:
- exposure levels in the rabbit, however, exceeded clinical exposure at the beginning of dosing (during organogenesis), but subsequently declined due to autoinduction.
- ETR had no effect on offspring development in rats, during lactation and postweaning at doses ≤500mg/kg/dav (equivalent to clinical exposure levels).
- Clinical data in pregnant humans are limited, and ETR should not be used during pregnancy unless the potential benefit justifies the potential risk.

Supported by Tibotec