Satellite groups:	N/A

Daily Dose (mg/kg/day)		0 (Control)	15	30	90
Dams/Dose					
Number of Females		24	24	32	34
Number of TK Females (pregnant)		6 (3)	7 (3)	6 (4)	6 (3)
Toxicokinetics		2	3	4	5
AUC_{last} (ng•h/mL)	First (GD 6)	<LLOQ	214.80	507.50	2333.00
	Last (GD 19)	<LLOQ	374.67	915.75	4649.33
C_{max} (ng/mL)	First (GD 6)	<LLOQ	31.53	59.25	248.43
	Last (GD 19)	<LLOQ	66.37	163.98	445.67

Safety Margins

Table 9. Applicant - Comparison of Pharmacokinetic Parameters for Taletrectinib Across Nonclinical Species at the NOAEL and HNSTD (or STD_{10}) With Human Participants at 600 mg (Once Daily)

Species	Rat		Rat (Pregnant)	Rabbit (Pregnant)	Human
Study Duration	**Fertility**		**EFD**	**EFD**	**-**
	Male	**Female**	**Female**	**Female**	**-**
HNSTD (mg/kg/day)	-	-	-	-	600 mg
NOAEL (mg/kg/day)	25	100	73.5[e]	<15	-
C_{max} (ng/mL)	289.328[b]	823.517[b]	982.200[c]	66.37[d]	668
Margin of Exposure[a]	0.4	1.2	1.5	0.1	-
$AUC_{0\text{-}24h}$ (ng·h/mL)	3758.667[b]	12784.837[b]	12339.190[c]	374.67[d]	13100 (AUC_{tau})

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

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Margin of Exposure[a]	0.3	1.0	0.9	0.03	-

Abbreviations: AUC, area under the concentration-time curve; $AUC_{0\text{-}24h}$, area under the concentration-time curve from 0 to 24 hours; C_{max}, maximum concentration; EFD, embryo-fetal development; HNSTD, highest non-severely toxic dose; NOAEL, no observed adverse effect level; STD_{10}, severely toxic dose in 10% of the animals
Source: Module 2.6.6 and Report Nos. 02049-20003 (Rat fertility), 02049-20004 (Rat EFD), T2102034 (Rabbit EFD). Pharmacokinetic data represent repeat-dose exposure at the end of the dosing period. The pharmacokinetic data for human subjects are from Clinical Trial DS-6051-A-J102 (Section 9.2.1.2 in clinical study report) based on exposure at 600 mg QD.

[a] The margin of exposure was determined as the ratio of exposure (AUC or C_{max} of Taletrectinib) in animals to the exposure in humans.
[b] The last dosing day was at GD6 for female rats and Day 83 for male rats.
[c] The last dosing day was at GD17 for female rats.
[d] The last dosing day was at GD19 for female rabbits and the data $AUC_{0\text{-}24h}$ was presented.
[e] The dose levels used by salt form was 100 mg/kg, corresponding to 73.5 mg/kg in free form of taletrectinib, see Report No.02049-20004 (Section 7.1.2).

Table 10. Applicant - Comparison of Pharmacokinetic Parameters for Taletrectinib Across Nonclinical Species at the Highest Dose Tested and Human Pharmacokinetic Values at 600 mg (Once Daily)

Species	**Rat**		**Rat (Pregnant)**	**Rabbit (Pregnant)**	**Human**
Study Duration	**Fertility**		**EFD**	**EFD**	**-**
	Male	**Female**	**Female**	**Female**	**-**
High dose (mg/kg/day)	60	100	73.5[e]	90	600 mg
C_{max} (ng/mL)	584.198[b]	823.517[b]	982.200[c]	445.67[d]	668
Margin of Exposure[a]	0.9	1.2	1.5	0.7	-
$AUC_{0\text{-}24h}$ (ng·h/mL)	9599.867[b]	12784.837[b]	12339.190[c]	4649.33[d]	13100 (AUC_{tau})
Margin of Exposure[a]	0.7	1.0	0.9	0.4	-

Abbreviations: AUC, area under the concentration-time curve; $AUC_{0\text{-}24h}$, area under the concentration-time curve from 0 to 24 hours; C_{max}, maximum concentration; EFD, embryo-fetal development.
Source: Module 2.6.6 and Report Nos. 02049-20003 (Rat fertility), 02049-20004 (Rat EFD), T2102034 (Rabbit EFD). Pharmacokinetic data represent repeat-dose exposure at the end of the dosing period. The pharmacokinetic data for human subjects are from Clinical Trial DS-6051-A-J102 (Section 9.2.1.2 in clinical study report) based on exposure at 600 mg QD.

[a] The margin of exposure was determined as the ratio of exposure (AUC or C_{max} of Taletrectinib) in animals to the exposure in humans.
[b] The last dosing day was at GD6 for female rats and Day 83 for male rats.
[c] The last dosing day was at GD17 for female rats.
[d] The last dosing day was at GD19 for female rabbits and the data $AUC_{0\text{-}24h}$ was presented.
[e] The dose levels used by salt form was 100 mg/kg, corresponding to 73.5 mg/kg in free form of taletrectinib, see Report No.02049-20004 (Section 7.1.2).

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