#M1280

Toxicokinetics of ETI-385 and its Components ETI-382 and ETI-383, a Serotonin 5-HT$_{1A}$ Receptor Agonist for Treatment of Nausea and Vomiting, Following Subcutaneous Injection of ETI-385 to CD-1 Mice and Beagle Dogs

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Abstract

Purpose:

To assess the toxicokinetics (TK) of ETI-382 and ETI-383 in CD-1 mice and Beagle dogs following subcutaneous injection of ETI-385. ETI-385, an 8-to-1 fixed ratio combination of the (S)-(-) and (R)-(+) enantiomers 8-hydroxy-2-dipropylaminotetralin hydrobromide (ETI-383 and ETI-382, respectively), is a serotonin 5-HT$_{1A}$ receptor agonist. Other serotonin receptors are also involved and strongly influence the efficacy and side effect profile. Preclinical models demonstrated ETI-385 efficacy in treatment of nausea and vomiting. Clinical studies are expected to begin early 2013.

Methods:

Four groups of mice and dogs received 7-daily subcutaneous injection of ETI-385 at 0, 3, 10 or 30 mg/kg/day to mice and 0, 0.3, 1 or 3 mg/kg/day to dogs. Blood samples were collected at predetermined times on Days 1 and 7. Plasma was assayed for ETI-382 and ETI-383 by a validated assay. TK parameters were determined by model-independent methods.

Results:

Day 1 ETI-383 C_{max} values in mice were 566, 1260 and 2910 ng/mL, in males and 472, 1120 and 2520 ng/mL, in females for 3, 10 or 30 mg/kg doses, respectively. Corresponding AUC_{0-24} values were 464, 1300 and 4030 ng•h/mL for males and 342, 1200 and 3750 ng•h/mL for females. Apparent $T_{1/2}$ ranged from 0.209 to 0.472 hour. In dogs, Day 1 ETI-383 mean C_{max} values were 66.3, 185 and 936 ng/mL, in males and 71.3, 187 and 573 ng/mL, in females for 0.3, 1 and 3 mg/kg, respectively. Corresponding mean AUC_{0-24} values were 134, 427 and 1600 ng•h/mL for males and 141.3, 372 and 1250 ng•h/mL for females. Apparent mean $T_{1/2}$ ranged from 0.718 to 1.38 hours. All Day 7 C_{mean} AUC and $T_{1/2}$ values were approximately equal to Day 1 values. In both species, Days 1 and 7 ETI-382 and ETI-383 TK exposure increased as a function of ETI-385 doses and was slightly higher in males. The ETI-382 C_{max} and AUC values were ~8 to 12 fold lower than those for ETI-383.

Conclusions:

In mice and dogs, ETI-382 and ETI-383 exposure increased as a function of ETI-385 dose and was slightly higher in males. Both enantiomers didn't accumulate following repeated doses. ETI-382 exposure was ~8.3 - 12.5% of ETI-383 exposure.

Purpose

To evaluate the toxicokinetics (TK) of ETI-382 and ETI-383 in CD-1 mice and Beagle dogs following subcutaneous injection of ETI-385. ETI-385, an 8-to-1 fixed ratio combination of the (S)-(-) and (R)-(+) enantiomers 8-hydroxy-2 dipropylaminotetralin hydrobromide (ETI-383 and ETI-382, respectively), is a serotonin 5-HT$_{1A}$ receptor agonist.

Introduction

ETI-385 is a serotonin 5-HT$_{1A}$ receptor agonist and is a novel antiemetic against drug induced emesis.

Other serotonin receptors are also involved and strongly influence the efficacy and side effect profile.

Preclinical models demonstrated ETI-385 efficacy in treatment of nausea and vomiting.

Clinical studies are expected to begin early 2013.

Methods

Study Design

Four groups of mice and dogs received 7-daily subcutaneous injections of ETI-385 at 0, 3, 10 or 30 mg/kg/day to mice and 0, 0.3, 1 or 3 mg/kg/day to dogs. Blood samples were collected at predetermined times on Days 1 and 7.

Analytical Method

Plasma was assayed for ETI-382 and ETI-383 by a validated assay.

TK Analysis

The TK parameters were determined by standard model independent methods (Gibaldi and Perrier, 1982) using Phoenix WinNonlin Professional Version 6.1 (Pharsight Corp., Mountain View, CA).

Figure 1

ETI-382 and ETI-383 Mean Plasma Concentration-Time Profiles in Mice on Days 1 and 7 Following Once Daily Subcutaneous Doses of ETI-385

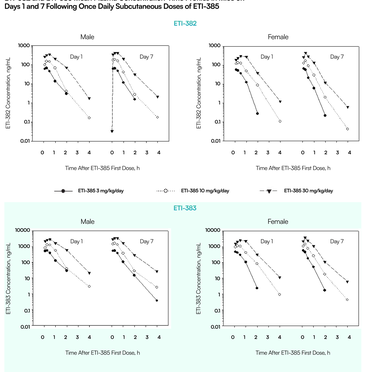

Figure 2

ETI-382 and ETI-383 C_{max} Versus Dose in Mice on Days 1 and 7 Following Subcutaneous Doses of ETI-385

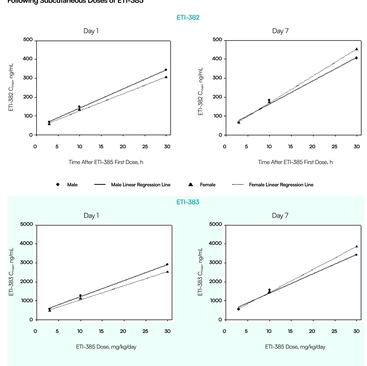

Figure 3

ETI-382 and ETI-383 AUC_{0-24} Versus Dose in Mice on Days 1 and 7 Following Once Daily Subcutaneous Doses of ETI-385

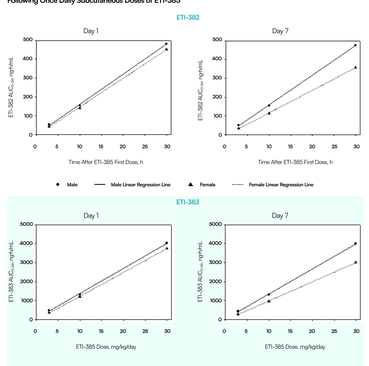

Figure 4

ETI-382 and ETI-383 Mean Plasma Concentration-Time Profiles in Dogs on Days 1 and 7 Following Once Daily Subcutaneous Doses of ETI-385

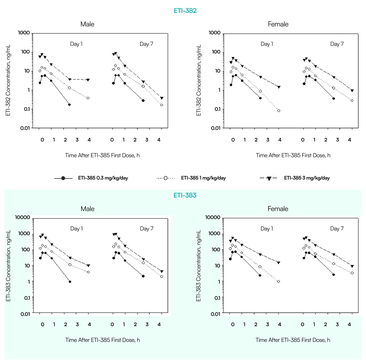

Figure 5

ETI-382 and ETI-383 Mean C_{max} Versus Dose in Dogs on Days 1 and 7 Following Subcutaneous Doses of ETI-385

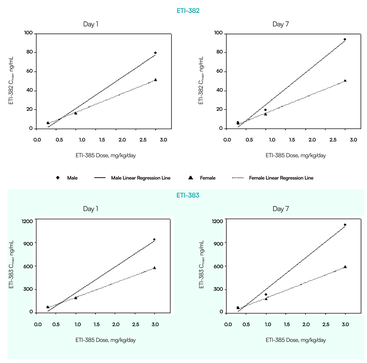

Figure 6

ETI-382 and ETI-383 Mean AUC_{0-24} Versus Dose in Dogs on Days 1 and 7 Following Once Daily Subcutaneous Doses of ETI-385

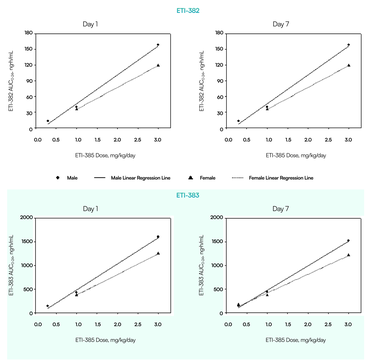

Table 1

Summary of ETI-382 and ETI-383 TK Parameters in Mice Following Once Daily Subcutaneous Doses of ETI-385

Day	ETI-385 Dose mg/kg/day	Male			Female		
		3	10	30	3	10	30
		ETI-382					
1	C_{max}, ng/mL	67.4	147	345	1.25	1.31	1.36
	T_{max}, h	0.250	0.250	0.500	1.00	1.00	1.00
	AUC_{0-24}, ng•h/mL	53.1	153	482	948	3,160	8,490
	$AUC_{0-\infty}$, ng•h/mL	53.1	153	483	920	3,060	8,160
	AUC_{last}, ng•h/mL	51.6	153	483	948	3,160	8,490
	$T_{1/2}$, h	0.395	0.351	0.428	920	3,060	8,160
	C_{max} Sex Ratio (M/F)	1.17	1.09	1.13	-	-	-
	AUC_{0-24} Sex Ratio (M/F)	1.26	1.09	1.06	-	-	-
7	C_{max}, ng/mL	64.2	183	0.500	1.00	1.00	1.00
	T_{max}, h	0.250	0.250	0.250	0.0833	0.250	0.250
	AUC_{0-24}, ng•h/mL	49.5	153	475	33.5	113	358
	AUC_{last}, ng•h/mL	49.5	153	476	33.5	113	358
	$T_{1/2}$, h	0.309	0.361	0.457	0.220	0.315	0.389
	C_{max} Sex Ratio (M/F)	0.968	1.05	0.894	-	-	-
	AUC_{0-24} Sex Ratio (M/F)	1.48	1.35	1.33	-	-	-
	Day 7/Day 1 C_{max} Ratio	0.953	1.24	1.38	1.35	1.29	1.48
	Day 7/Day 1 AUC_{0-24} Ratio	0.932	1.00	0.986	0.796	0.801	0.789
		ETI-383					
1	C_{max}, ng/mL	566	1,260	2,910	472	1,120	2,520
	T_{max}, h	0.250	0.250	0.500	0.0833	0.250	0.500
	AUC_{0-24}, ng•h/mL	464	1,300	4,020	342	1,200	3,750
	$AUC_{0-\infty}$, ng•h/mL	464	1,300	4,030	342	1,200	3,750
	AUC_{last}, ng•h/mL	451	1,300	4,030	341	1,200	3,750
	$T_{1/2}$, h	0.415	0.395	0.472	0.209	0.344	0.398
	C_{max} Sex Ratio (M/F)	1.20	1.13	1.15	-	-	-
	AUC_{0-24} Sex Ratio (M/F)	1.36	1.08	1.07	-	-	-
	ETI-383/ETI-382 C_{max} Ratio	8.40	8.57	8.43	8.17	8.30	8.24
	ETI-383/ETI-382 AUC_{0-24} Ratio	8.74	8.50	8.34	8.12	8.51	8.26
7	C_{max}, ng/mL	544	1,580	5,410	570	1,470	3,860
	T_{max}, h	0.250	0.250	0.500	0.0833	0.250	0.250
	AUC_{0-24}, ng•h/mL	424	1,310	3,980	276	949	3,010
	AUC_{last}, ng•h/mL	424	1,310	4,000	276	949	3,010
	$T_{1/2}$, h	0.369	0.369	0.516	0.220	0.324	0.401
	C_{max} Sex Ratio (M/F)	0.954	1.07	0.883	-	-	-
	AUC_{0-24} Sex Ratio (M/F)	1.54	1.38	1.33	-	-	-
	Day 7/Day 1 C_{max} Ratio	0.961	1.25	1.17	1.21	1.31	1.53
	Day 7/Day 1 AUC_{0-24} Ratio	0.914	1.01	0.993	0.807	0.791	0.803
	ETI-383/ETI-382 C_{max} Ratio	8.47	8.63	8.40	8.24	8.45	8.50
	ETI-383/ETI-382 AUC_{0-24} Ratio	8.57	8.56	8.40	8.24	8.40	8.41

Table 2

Summary of ETI-382 and ETI-383 TK Parameters in Dogs Following Once Daily Subcutaneous Doses of ETI-385

Day	ETI-385 Dose mg/kg/day	Male			Female		
		0.3	1	3	0.3	1	3
		ETI-382					
1	C_{max}, ng/mL	5.99	15.9	79.5	6.20	16.3	51.4
	T_{max}, hr	1.00	0.500	0.500	1.00	0.500	0.500
	AUC_{0-24}, ng•h/mL	13.6	38.3	153	14.3	34.4	119
	$AUC_{0-\infty}$, ng•h/mL	12.6	39.4	158	NC	35.1	119
	AUC_{last}, ng•h/mL	12.6	39.2	156	NC	35.0	119
	$T_{1/2}$, hr	0.832	1.38	1.03	NC	0.960	1.35
	C_{max} Sex Ratio (M/F)	0.966	0.975	1.55	-	-	-
	AUC_{0-24} Sex Ratio (M/F)	NC	1.12	1.53	-	-	-
7	C_{max}, ng/mL	6.10	19.7	94.1	5.57	15.0	50.4
	T_{max}, hr	0.500	0.500	0.500	1.00	0.500	0.500
	AUC_{0-24}, ng•h/mL	12.3	39.3	143	14.2	33.5	113
	AUC_{last}, ng•h/mL	12.5	39.8	144	14.6	35.0	116
	$T_{1/2}$, hr	0.782	1.07	1.03	0.819	1.04	1.23
	C_{max} Sex Ratio (M/F)	1.10	1.31	1.87	-	-	-
	AUC_{0-24} Sex Ratio (M/F)	0.856	1.14	1.24	-	-	-
	Day 7/Day 1 C_{max} Ratio	1.02	1.24	1.18	0.898	0.920	0.981
	Day 7/Day 1 AUC_{0-24} Ratio	0.992	1.01	0.971	NC	0.997	0.975
		ETI-383					
1	C_{max}, ng/mL	66.3	185	936	71.3	187	573
	T_{max}, hr	0.500	0.500	0.500	1.00	0.500	0.500
	AUC_{0-24}, ng•h/mL	126	417	1,580	148	366	1,210
	$AUC_{0-\infty}$, ng•h/mL	134	427	1,600	NC	372	1,250
	AUC_{last}, ng•h/mL	134	425	1,600	NC	371	1,250
	$T_{1/2}$, hr	0.718	1.10	1.06	NC	0.911	1.38
	C_{max} Sex Ratio (M/F)	0.930	0.989	1.63	-	-	-
	AUC_{0-24} Sex Ratio (M/F)	NC	1.15	1.28	-	-	-
	ETI-383/ETI-382 C_{max} Ratio	11.1	11.6	11.8	11.5	11.5	11.1
	ETI-383/ETI-382 AUC_{0-24} Ratio	10.6	10.8	10.1	NC	10.6	10.5
7	C_{max}, ng/mL	68.0	234	1,120	64.3	177	587
	T_{max}, hr	0.500	0.500	0.500	1.00	0.500	0.500
	AUC_{0-24}, ng•h/mL	114	430	1,520	152	351	1,200
	AUC_{last}, ng•h/mL	135	454	1,520	168	367	1,220
	$T_{1/2}$, hr	0.930	1.14	1.03	0.784	1.02	1.25
	C_{max} Sex Ratio (M/F)	1.06	1.32	1.91	-	-	-
	AUC_{0-24} Sex Ratio (M/F)	0.804	1.38	1.25	-	-	-
	Day 7/Day 1 C_{max} Ratio	1.03	1.26	1.20	0.902	0.947	1.02
	Day 7/Day 1 AUC_{0-24} Ratio	1.01	1.02	0.950	NC	0.987	0.976
	ETI-383/ETI-382 C_{max} Ratio	11.1	11.9	11.9	11.5	11.8	11.6
	ETI-383/ETI-382 AUC_{0-24} Ratio	10.8	10.9	10.6	11.5	10.5	10.5

* Expressed as median; ^ Expressed as harmonic mean; NC - Not calculated

Results

Following subcutaneous injection of ETI-385, ETI-382 and ETI-383 were readily measurable in plasma of both species with T_{max} values ranging from 0.0833 to 0.500 h in mice and from 0.500 to 1.00 h in dogs (Tables 1 and 2 and Figures 1 and 4).

In mice, Day 1 ETI-383 C_{max} values were 566, 1260 and 2910 ng/mL, in males and 472, 1120 and 2520 ng/mL, in females for 3, 10 or 30 mg/kg doses, respectively. Corresponding AUC_{0-24} values were 464, 1300 and 4030 ng•h/mL for males and 342, 1200 and 3750 ng•h/mL for females. Apparent $T_{1/2}$ ranged from 0.209 to 0.472 hour. All Day 7 PK parameters values of ETI-383 (T_{max}, C_{max}, AUC and $T_{1/2}$) were approximately equal to Day 1 values (Table 1). ETI-383 C_{max} and AUC values were ~8 - 9x higher than those of ETI-382 (Table 1). ETI-382 and ETI-383 C_{max} and AUC increased with ETI-385 doses in a dose proportional manner in both sexes in mice (Table 1 and Figure 2).

In dogs, Day 1 ETI-383 mean C_{max} values were 66.3, 185 and 936 ng/mL, in males and 71.3, 187 and 573 ng/mL, in females for 0.3, 1 and 3 mg/kg, respectively.

Corresponding mean AUC_{0-24} values were 134, 427 and 1600 ng•h/mL for males and not calculated (NC), 372 and 1250 ng•h/mL for females (Table 2). Apparent mean $T_{1/2}$ ranged from 0.718 to 1.38 hours. Day 1 C_{max} and AUC_{0-24} of ETI-383 in males increased with ETI-385 doses in a dose proportional at the two lower doses (0.3 and 1 mg/kg), and greater than dose proportional at the highest dose (3 mg/kg) (Table 2 and Figures 5 and 6). In females, the increases were dose proportional at all doses. Days 1 and 7 plasma exposures of ETI-382 increased as a function of ETI-385 doses in a dose proportional at the two lower doses, and greater than dose proportional at the highest dose in both sexes (Table 2 and Figures 5 and 6). ETI-383 C_{max} and AUC values were ~9 - 12x higher than those of ETI-382 (Table 2).

In both species, Tmax and $T_{1/2}$ values for both enantiomers did not change due to the increase in ETI-385 dose or repeated dosing. No accumulation of either enantiomer was observed following 7 days of repeated daily dosing (Tables 1 and 2 and Figures 1 through 6).

Conclusions

In both species, ETI-382 and ETI-383 C_{max} and AUC increased with ETI-385 doses. T_{max} and $T_{1/2}$ values for both enantiomers did not change due to the increase in ETI-385 dose or repeated dosing. No accumulation of either enantiomer was observed following 7 days of repeated daily dosing. The absence of accumulation is consistent with the short $T_{1/2}$ of both enantiomers (<1.4h). ETI-382 and ETI-383 displayed a slightly higher plasma exposure in males than females.

References

Gibaldi, M. and Perrier, D., 1982. Pharmacokinetics, Second Edition, Marcel Dekker, Inc., New York.