April 12, 2013

VIA HAND DELIVERY
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2013-P-0198
Citizen Petition, Supplement No. 1

Takeda Pharmaceuticals U.S.A., Inc. ("Takeda") respectfully submits this supplement to the citizen petition submitted on February 15, 2013 and assigned Docket No. FDA-2013-P-0198 (the Petition).

In its citizen petition, Takeda referred to data contained in Clinical Study Report M93-006, titled "Dose Response Evaluation of Multiple Doses of Lansoprazole (ABT-006) Using 24-Hour Determinations of pH," submitted to FDA under NDA 20-406, Supplement 002, Amendment 001 (Aug. 1995) (Study Report M93-006). *See* Petition at 13-14 and n.58. This supplement clarifies for the agency that the comparison of the 30 mg BID and 60 mg QD doses of lansoprazole, discussed and shown on pages 13-14 of the Petition, was based on data from Study M93-006. These data are contained in Study Report M93-006, as referenced in Takeda's petition, on file with the agency at pages 47 and 52. *See* Supp. Tab 1, Study Report M93-006 at 47 (Table 9.1.a, 30 mg BID column) and 52 (Table 9.1.b, 60 mg QD column). However, the comparison of the 30 mg BID data and the 60 mg QD data from Study M93-006 discussed in the petition is not contained or discussed in Study Report M93-006. The Study tested and compared a multiple-dose regimen of 15 mg lansoprazole and single and multiple-dose regimens of 30 mg and 60 mg lansoprazole, including 30 mg BID and 60 mg QD, but it did not include a direct comparison of the 30 mg BID dose with the 60 mg QD dose.

The observed difference in percent time pH > 4 between these two dose regimens helped inform Takeda's thinking on the development of the product that eventually became DEXILANT (dexlansoprazole) delayed-release capsules. This difference was not based on a direct comparison under Study M93-006 and was not subjected to a pre-specified statistical analysis. It was based only on the observed numerical differences in pH control between the 30 mg BID and 60 mg QD dosing regimens in the different dosing groups tested under the Study. Thus, the statement in the petition that "[t]he percent time pH > 4 was *statistically* different and greater for the 30 mg BID regimen as compared to the 60 mg QD regimen for the entire 24 hour post-dose period and for the nighttime hours" must be clarified. *See* Petition at 14 (emphasis added). The percent time pH > 4 for these two doses was numerically different for the 24 hour period and the

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nighttime hours, but the statistical significance of this difference was not assessed in the Study. We regret any confusion this may have caused.

For the agency's convenience, in Table 1 below we have presented the numerical comparison of lansoprazole 30 mg BID and 60 mg QD based on the data contained in Study Report M93-006, with the data for the 24 hour period and the nighttime hours highlighted.

Table 1. Analysis of 24-Hour Intragastric Mean pH Determinations
(Study Report M93-006, Table 9.1.a, Table 9.1.b)

Interval	Mean pH	
	30 mg BID (Dosing Group 1)	60 mg QD (Dosing Group 2)
Total 24 hours	**5.07**	**4.45**
0830-1330	4.87	4.96
1330-1830	4.95	5.13
1830-2300	**5.36**	**4.82**
2300-0800	**5.12**	**3.61**
Interval	% Time pH > 4	
	30 mg BID (Dosing Group 1)	60 mg QD (Dosing Group 2)
Total 24 hours	**75.33**	**63.51**
0830-1330	70.31	76.86
1330-1830	77.50	81.75
1830-2300	**87.50**	**79.48**
2300-0800	**71.88**	**39.48**

In 2003, the data from M93-006 were re-evaluated to assess the pH control of BID dosing relative to QD dosing as a way to determine the feasibility and potential pharmacodynamic effect of a modified-release formulation of lansoprazole. As part of this assessment, the pH profiles of 30 mg BID and 60 mg QD were evaluated and compared as depicted in Figure 1 of the Petition (at page 14). These data are illustrated in separate plots in Study Report M93-006 at pages 44 and 49 of the Study Report. *See* Supp. Tab 1, Study Report M93-006 at 44 (Figure 9.1.a, 30 mg BID) and 49 (Figure 9.1.c, 60 mg QD). In parallel, the feasibility of creating a formulation containing only the R-enantiomer of lansoprazole (dexlansoprazole) was assessed. Based on the results of these feasibility assessments, the development of a modified-release formulation of dexlansoprazole was initiated. *See* Petition at 14-15.

For additional clarification, the pharmacokinetic data comparing 60 mg QD dexlansoprazole modified-release to 30 mg QD lansoprazole, displayed in Figure 2 of the Petition (at page 17), were drawn from Vakily, M., *et al.*, Curr. Med. Res. Opin. (2009) 25: 627-638, 631 (Figure 1A), included in the Petition as Tab 11 (page 10 n.43).

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VERIFICATION

I certify that, to my best knowledge and belief: (a) I have not intentionally delayed submission of this document or its contents; and (b) the information upon which I have based the action requested herein first became known to me on or about March 28, 2013. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: None, other than my compensation as an employee of Takeda. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,

Michael Kukulka
Principal Scientist, Clinical Pharmacology
Takeda Pharmaceuticals U.S.A., Inc.

Enclosure

Cc: Kathleen Uhl, M.D.
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SUPP.
TAB 1

CLINICAL/STATISTICAL REPORT

DOSE RESPONSE EVALUATION OF MULTIPLE DOSES OF LANSOPRAZOLE (ABT-006) USING 24-HOUR DETERMINATIONS OF pH

ABT-006

Study No. M93-006

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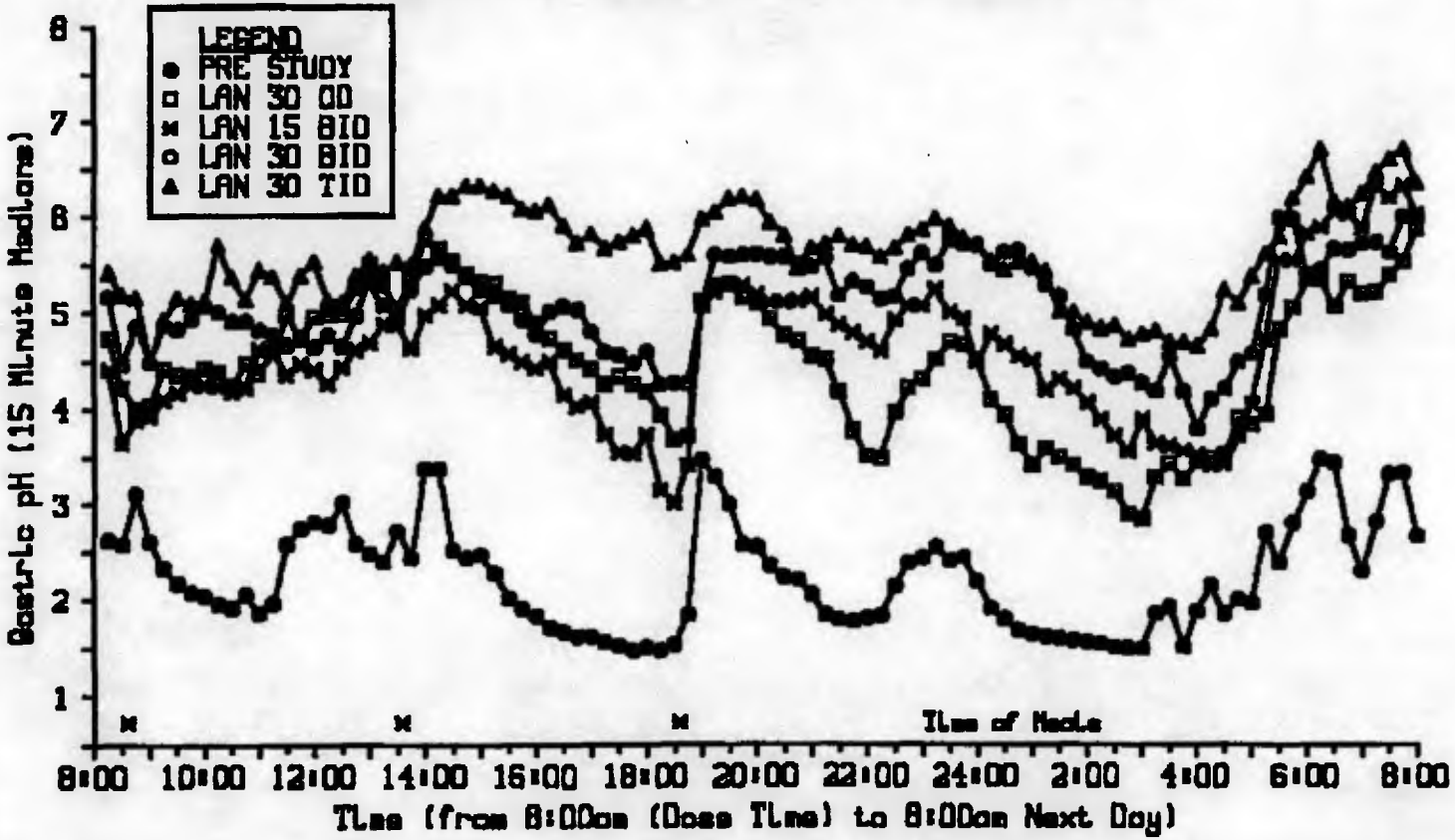
Figure 8.1.a
Intragastric pH Levels on Day 5 for Dosing Group 1



No significant differences were observed between the 30 mg QD and the 15 mg BID regimens.

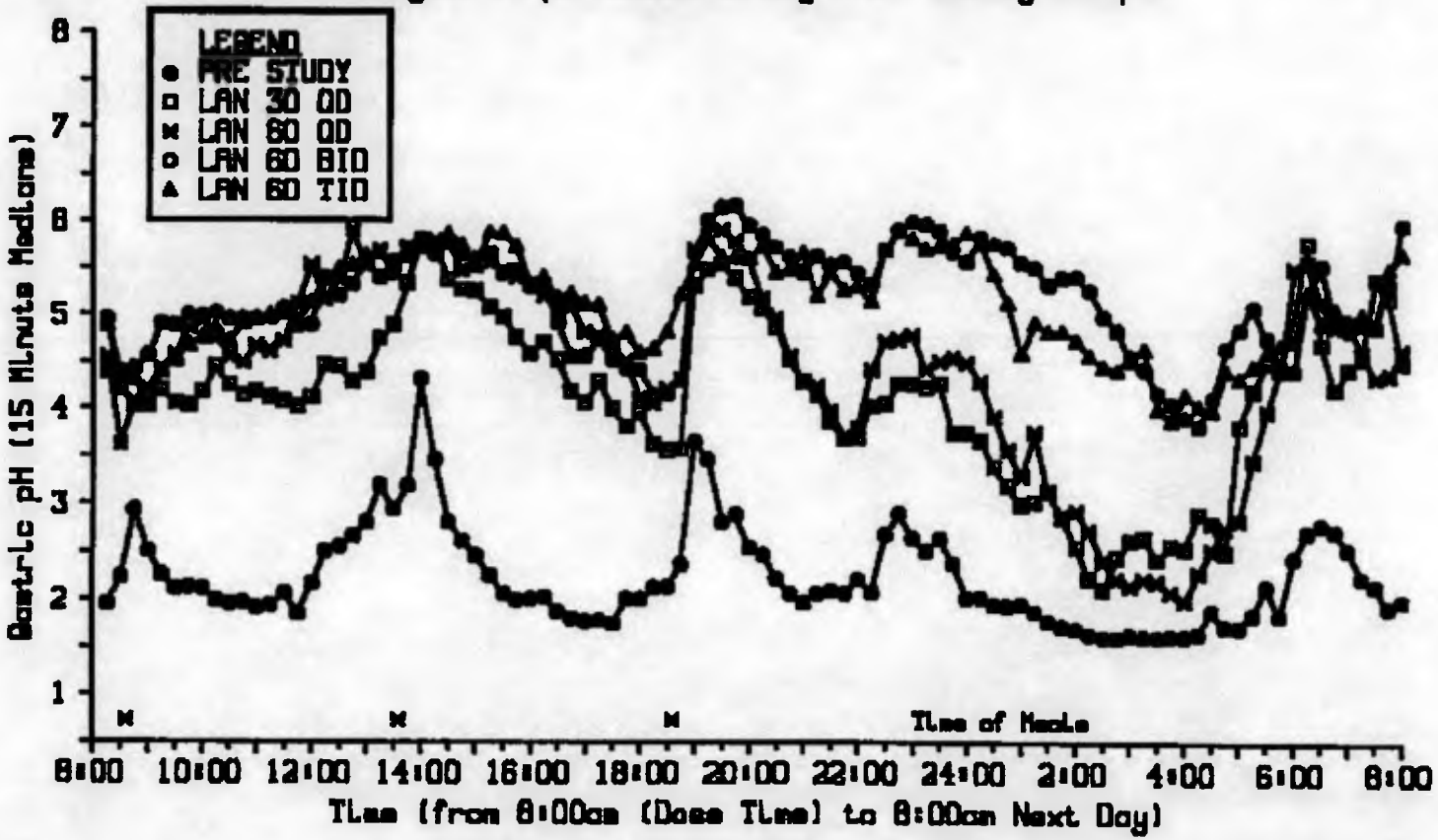
Table 9.1.a

Analysis of 24-Hour Intragastric Adjusted Mean pH Determinations for Dosing Group 1

Variable Interval	Adjusted Mean Values			
	30 mg QD (N=16)	15 mg BID (N=16)	30 mg BID (N=16)	30 mg TID (N=16)†
Mean pH				
Total 24 hours	4.47	4.57	5.07*	5.63*,+
0830-1330	4.67	4.37	4.87	5.25+
1330-1830	4.82	4.28	4.95+	5.93*,+,&
1830-2300	4.47	4.93	5.36*	5.82*,+
2300-0800	4.15	4.70	5.12*	5.54*,+
Percent of time pH >3				
Total 24 hours	72.20	74.73	85.16	91.52*,+
0830-1330	77.50	76.25	85.00	88.48
1330-1830	81.88	72.81	87.81	96.88+
1830-2300	82.29	88.59	94.10	97.22*
2300-0800	59.38	69.44	80.38*	87.67*,+
Percent of time pH >4				
Total 24 hours	62.30	62.67	75.33	86.58*,+
0830-1330	68.75	57.50	70.31	81.32+
1330-1830	72.81	57.19	77.50+	94.38*,+
1830-2300	70.49	79.82	87.50*	92.36*
2300-0800	49.31	61.28	71.88*	81.94*,+
Percent of time pH >5				
Total 24 hours	43.29	46.77	58.53*	76.62*,+,&
0830-1330	40.00	34.06	47.81	64.49*,+,&
1330-1830	56.56	41.25	57.50	89.06*,+,&
1830-2300	39.58	56.25	72.22*	85.07*,+
2300-0800	39.41	52.43	58.51*	71.35*,+
Percent of time pH >6				
Total 24 hours	20.31	23.00	28.39	44.69*,+,&
0830-1330	23.75	16.25	24.06	28.56
1330-1830	15.00	13.44	19.69	52.81*,+,&
1830-2300	7.29	15.28	25.00*	51.04*,+,&
2300-0800	26.56	35.59	36.11	43.06*

† N=15 for the total 24-hour and 0830-1330 time intervals.
* Significantly ($p \leq 0.05$) greater increase than the 30 mg QD regimen.
+ Significantly ($p \leq 0.05$) greater increase than the 15 mg BID regimen.
& Significantly ($p \leq 0.05$) greater increase than the 30 mg BID regimen.

Figure 9.1.a
Intragastric pH Levels on Day 5 for Dosing Group 2



pH was above 5 and 6 was observed in these regimens when compared to the 60 mg QD regimen.

Such differences were not observed between the 60 mg BID and 60 mg TID regimens.

Table 9.1.b

Analysis of 24-Hour Intragastric Adjusted Mean pH Determinations for Dosing Group 2

Variable Interval	Adjusted Mean Values			
	30 mg QD (N=16)	60 mg QD (N=16)	60 mg BID (N=16)	60 mg TID (N=16)
Mean pH				
Total 24 hours	4.13	4.45	5.19*,+	5.13*,+
0830-1330	4.25	4.96*	5.10*	4.94*
1330-1830	4.63	5.13	5.11	5.32*
1830-2300	4.49	4.82	5.66*,+	5.50*,+
2300-0800	3.59	3.61	5.09*,+	4.96*,+
Percent of time pH >3				
Total 24 hours	68.57	74.92	89.78*,+	84.16*
0830-1330	78.72	91.20	95.59*	83.11
1330-1830	84.42	90.31	88.40	87.12
1830-2300	81.44	89.66	98.08*	90.29
2300-0800	48.19	51.15	84.53*,+	80.72*,+
Percent of time pH >4				
Total 24 hours	52.59	63.51*	82.72*,+	77.37*,+
0830-1330	54.44	76.86*	87.49*	76.02*
1330-1830	69.78	81.75	81.40	82.97*
1830-2300	65.91	79.48*	95.77*,+	85.66*
2300-0800	35.70	39.48	75.83*,+	71.84*,+
Percent of time pH >5				
Total 24 hours	33.27	40.02	62.84*,+	63.01*,+
0830-1330	25.94	42.23*	49.97*	53.92*
1330-1830	47.95	60.26	63.90	69.90*
1830-2300	41.53	48.53	83.84*,+	78.67*,+
2300-0800	24.65	23.64	59.66*,+	57.16*,+
Percent of time pH >6				
Total 24 hours	16.64	19.43	28.67*,+	32.96*,+
0830-1330	16.76	23.26	20.38	25.93*
1330-1830	15.04	29.43*	26.18	41.40*,&
1830-2300	11.58	12.78	35.50*,+	37.89*,+
2300-0800	18.89	14.53	30.49*,+	28.86*,+

* Significantly ($p \leq 0.05$) greater increase than the 30 mg QD regimen.
\+ Significantly ($p \leq 0.05$) greater increase than the 60 mg QD regimen.
& Significantly ($p \leq 0.05$) greater increase than the 60 mg BID regimen.