Errata Sheet (dated 9/7/2005)
to
FDA Background Package
September 9, 2005
Endocrinologic and Metabolic Advisory Committee Meeting
Pargluva™ (muraglitazar)
NDA 21-865

The enclosed page replaces page 13 of the original FDA statistical review for Pargluva (muraglitazar, NDA 21-865). The new analyses include the re-adjudicated cardiovascular (CV) death in a placebo patient. The new results include revised p-values and revised relative risks (RR). In particular, the new estimates for RR of 2.0 and 5.9 for CV deaths in the muraglitazar 2.5 mg and 5 mg groups, respectively, replace the estimates of 4.5 and 19.8 from the original review.

It should be noted that the generated p-values are based on analyses of safety endpoints, total and CV deaths. Type 1 error control in the individual trials was limited to pre-specified efficacy endpoints. As such, the p-values for safety endpoints are nominal (unadjusted) p-values that may overstate the significance of the observed results since they do not account for the multiplicity of statistical tests that were performed.

Death and Cardiovascular Death

Table 7 displays total deaths and a subset of total deaths, namely, cardiovascular death by study. Patients in the monotherapy studies were to be 'naïve' to antidiabetic drug, hence dissimilar in disease progression to patients in the combination studies who were inadequately controlled with sulfonylurea or metformin. The phase 3 monotherapy study had no extension period and no deaths. The combination studies were all phase 3 studies with an ongoing extension phase.

Table 7a presents nominal 2-sided 95% p values using Exact trend tests for Poisson rates on person-year data, log rank tests on exact event times (Kaplan-Meier), and Exact Cochran Armitage trend tests on the incident rates. The tests were stratified by the 3 add on studies with the pioglitazone 30 mg group combined with the placebo group. P-values from the pooled analysis were similar to the stratified analysis. The sponsor reported relative risks of 1.7 and 4.6 for total death and 2.0 and 5.9 for CV death, for muraglitazar 2.5 mg and 5 mg respectively.

Table 7 Death and CV death

Study	Dose (mg)	n	Person-year	Death #	CV death
CV168006 Dose ranging	Mur 0.5	236	72.87	0	0
Monotherapy	Mur 1.5	259	409.70	2 (0.77%)	0
Mur 0.5 control	Mur 5	245	517.06	1 (0.41%)	0
	Mur 10	249	623.64	1 (0.40%)	0
	Mur 20	237	343.31	1 (0.42%)	1 (0.42%)
	Pio 15	251	331.49	1 (0.40%)	0
CV168018 Monotherapy Placebo	Placebo	115	43.84	0	0
control	Mur 2.5	111	46.60	0	0
	Mur 5	114	48.04	0	0
CV168021 Add-on Gly Placebo	Placebo+Gly	199	123.82	1 (0.50%)	1
control	Mur 2.5+Gly	191	206.49	0	0
	Mur 5+Gly	193	206.89	2 (1.04%)	1 (0.52%)
CV168022 Add-on Met Placebo	Placebo+Met	214	164.49	0	0
control	Mur2.5+Met	233	263.48	2 (0.86%)	1 (0.43%)
	Mur 5+Met	205	239.23	3 (1.46%)	1 (0.49%)
CV168025 Add-on Met	Pio 30+Met	572	440.03	1 (0.17%)	0
Active control	Mur 5+Met	587	468.84	6 (1.02%)	5 (0.85%)
Total Death				21	10

Mur = muraglitazar; Gly = glyburide; Pio = pioglitazone; Met = metformin

Table 7a Nominal p values for trend test on Death and CV death – stratified by add on studies

P value	All death	CV death
Person years (Poisson)	0.03	0.06
Time to event (days) (Log rank)	0.02	0.05
Incident rates (Cochran-Armitage)	0.009	0.04

The graphic displays show the lipid profiles and secondary outcome variables with the legend following the triglyceride graph. The primary endpoint for lipid outcomes was week 12 prior to which no change of lipid medication was allowed.