

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
200175

CROSS DISCIPLINE TEAM LEADER REVIEW



MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: July 15, 2010

FROM: Abraham Karkowsky, M.D., Ph.D., Team Leader, Division of Cardiovascular and Renal Products HFD-110

TO: Norman Stockbridge, M.D., Ph.D., Director, Division of Cardiovascular and Renal Products HFD-110

SUBJECT: Approvable recommendation for Tribenzor® (olmesartan medoxomil + amlodipine besylate + hydrochlorothiazide (NDA 200175, Daiichi Sankyo)

This memo¹ recommends approving the triple combination therapy of olmesartan medoxomil + amlodipine besylate + hydrochlorothiazide for the treatment of hypertension.

Each of the monotherapy components is approved. Two of the three dual combination therapies are approved (AML/HCTZ is not approved). The table below indicates the proposed dose strengths that the sponsor plans to market for the triple therapy.

Table 1: Formulations proposed for marketing

Formulation	OLM (mg)	AML (mg)	HCTZ (mg)
1	20	5	12.5
2	40	5	12.5
3	40	5	25
4	40	10	12.5
5	40	10	25

The drug should be labeled:

- ◆ As a product of convenience when it is substituted for the same dose of the individual components.

¹ The following abbreviations are used in this memo

OLM- olmesartan medoxomil AML-amlodipine besylate HCTZ- hydrochlorothiazide DMEPA-Division of medication Error Prevention and Analysis CMC-Chemistry and manufacturing controls	ONDQA- Office of new drugs quality assessment\ ARB-angiotensin receptor blocker d/c or d/c'd- discontinue or discontinued ABPM- Ambulatory blood pressure monitoring	BP- blood pressure SeDBP- seated diastolic blood pressure SeSBP- seated systolic blood pressure Cr- Creatinine
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- ◆ As a reasonable alternative when a subject has been treated with the maximally tolerated or labeled doses of two components and still requires additional antihypertensive effects. Under the latter circumstance, a decision should be made whether alternative monotherapy or combination therapy would be preferable to adding a third drug to the ongoing combination.
- ◆ After the maximally tolerated or labeled doses of two components that include: ARBs, dihydropyridine calcium channel blockers or thiazide diuretics, at their maximally tolerated or labeled doses, with a need for further blood pressure lowering effect. Prior to adding a third drug, a decision should be made as to whether the patient would be better served by either a different class of monotherapies or a different dual combination anti-hypertensive drug.

Triple therapy appears much too aggressive to be used as initial therapy. Adverse events for the triple therapy are greater than those of the dual therapies and there seems no compelling reason to routinely expose subjects to the safety risks.

There seems to be no credible scenario where more than one component of the triple combination should be increased at a time. It would seem that only the newly added component may require up-titration.

Adverse events and serious adverse events are increased during the time period subjects were on triple therapy compared to the dual therapies. Not surprisingly, hypotensive events (including vasodilatation events) were more prominent during treatment with triple therapy than with dual therapy. Renal dysfunction was also more common with triple therapy. The decrease in renal function was largely, but not completely, reversed after a reasonable post treatment washout.

The labeling for use of Tribenzor in selective populations needs some thought. Hepatic patients and elderly subjects should be started on the lowest dose of AML (2.5 mg), a dose not available with any of the Tribenzor formulations. Starting these subjects on triple therapy after inadequate response to OLM + HCTZ should not be done with Tribenzor, since the appropriate AML dose is not marketed.

Both OLM and HCTZ have PRECAUTIONS or WARNINGS for the use as monotherapy in patients with diminished renal function. The dual and triple therapies amplify the concern. The appropriate recommendations for these populations will be dealt with in the labeling.

The name Tribenzor was found acceptable by DMEPA. Additional comments by DMEPA, regarding the content of the label and content and structure of the packaging, is listed as Appendix A at the end of this review.

There are still some minor CMC issues that require some resolution. These issues are mostly requests for information and do not appear to be a major hurdle to approval. The information requests have already been transmitted to the sponsor by the CMC group and for completeness are listed in Appendix B of this review. All inspections have been

completed all facilities' inspections were "Acceptable". A shelf-life of 36 months was recommended by the CMC reviewers for all dose strengths and all packaging variations. A categorical exclusion from environmental assessment was requested and granted.

The market image formulation of the triple product, at both its high and low doses, was bioequivalent to both the high and lowest doses of the respective formulations used during the clinical trial. Bio-waivers were granted for the intermediate dose strengths of OLM/AML/HCTZ: 40/10/12.5 and 40/5/25. There does not to be a meaningful food effect and the combination may be administered irrespective to food.

The biometrics reviewer performed an elegant analysis modeling the data from the effects of triple therapy by including the already available from the two dual combination therapies (Azor; AML/OLM and Benicar HCT; OLM/HCTZ). There is, however, no approved AML/HCTZ formulation. The biometrics analysis consists of a change from baseline assessment. Despite the elegant modeled results, the utility of this information seems obscure to me. The drug will likely be used when there is inadequate response to maximally tolerated doses of two components. Having blood pressure effects that measure the excursion from pre-therapy does not seem terribly useful. The information most important is the effect of adding the third component of the combination to the highest dose of the other two components. This information can be determined from the key pivotal study.

There was a single 3-month oral gavage toxicology study in F344 rats that compared the effect of control, OLM/HCTZ combination and AML to three different doses of triple therapy, with the highest doses of the triple therapy corresponding to the single dose of OLM/HCTZ or AML that was used in this study. In general, the changes which were observed in histology were consistent with the effects observed for either AML or OLM/HCTZ comparator groups. The most striking features was renal effects that consisted of papillary mineralization, tubular regeneration and thickening of the arterial wall in the afferent artery. These effects were equivalently observed in the OLM/HCTZ animals.

The following reviews and memos were consulted in the formulation of this review:

- ◆ Memo from Richard Abate, RPh, MS, safety Evaluator; DMEPA regarding the Trade name Tribenzor® dated June 10, 2010.
- ◆ Memo from Richard Abate, RPh, MS, safety Evaluator; DMEPA regarding the proposed label, the review includes comments and recommendations for the label and containers dated June 3, 2010.
- ◆ Memo by Tapash K. Ghosh, Ph.D., ONDQA regarding biowaiver request for intermediate dose strengths of Tribenzor dated May 18, 2010.
- ◆ Pharmacology/Toxicology review by G. Jagadeesh, Ph.D. dated April 20, 2010.
- ◆ Inspection of site with no action indicated designation dated April 7, 2010.
- ◆ CMC Review number 1 by Prafull Shiromani, Ph.D., dated March 30, 2010.
- ◆ Joint Clinical Statistical review by Maryann Gordon, M.D., (clinical) and Fanhui Kong, Ph.D. (statistics) dated May 22, 2010.

- ◆ Additional analyses performed by Fanhui Kong, Ph.D. (statistics).
- ◆ Clinical Pharmacology Review by Rajanikanth Madabushi, Ph.D. (clinical Pharmacology), Jiang Liu, Ph.D., (Pharmacometrics) dated June 27, 2010.
- ◆ SEALD review of the label by Debbie Beitzell, BSN, dated June 21, 2010.

The approval of Tribenzor primarily rests on the results of study CS8635-A “A randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Co-Administration of Olmesartan Medoxomil, Amlodipine Besylate and Hydrochlorothiazide in Subjects with Hypertension”. The results of the study indicate that the addition of OLM to a combination of AML and HCTZ; HCTZ to a combination of OLM + AML; and AML to a combination of OLM + HCTZ the resultant effect of the triple therapy is greater than the effect of each of the dual therapies.

The study was a randomized double blind study that enrolled hypertensive patients with a seated blood pressure as measured by cuff of:

- ◆ BP \geq 140/100 or
- ◆ BP \geq 160/90

Patients, who were previously treated with antihypertensive medications, after a maximum of three weeks of washout, were allocated to one of the three possible dual therapies OLM + AML, OLM + HCTZ or AML + HCTZ for four weeks. Naïve (not previously treatment with hypertension medications) patients were maintained on placebo for two weeks and then randomized to one of the 3 possible dual therapies for two weeks. After an additional two weeks the naïve patients were randomized to one of the double combination therapies. At 4 weeks, each of the subjects, either naïve or non-naïve, had been treated with dual therapy from between 2-4 weeks, Subjects would then continue on one of the three two-combination therapies or be started at the maximum-labeled triple therapy. The triple therapy which was used is 40 mg for OLM, 10 mg for AML or the usual optimal dose of HCTZ 25 mg. These doses reflect the maximum labeled doses for OLM and AML. Although the current label for HCTZ suggests a maximal dose of up to 50 mg, the frequency of hypokalemia, hyperglycemia, hyperuricemia and hyperlipidemia becomes commensurately more important at the higher dose and the highest labeled dose of HCTZ is infrequently used. The randomized doses (either one of the two combinations or the triple combination) were continued till week 12.

The schematic diagram of the treatments and the number of subjects at each portion of the study is shown Figure 1.

Figure 1 Schematic of study dosing

Period II Treatment Assignments

	n	Day 1 to Week 2	Week 2 to Week 4	Week 4 to Week 12	
838 subjects	618	OM/AML/HCTZ 40/10/0 mg		OM/AML/HCTZ 40/10/0 mg (628 subjects)	
	naïve	10	OM/AML/HCTZ 0/0/0 mg		OM/AML/HCTZ 40/10/0 mg
	naïve	4	OM/AML/HCTZ 0/0/0 mg	OM/AML/HCTZ 40/10/0 mg	OM/AML/HCTZ 40/10/25 mg (210 subjects)*
	naïve	206	OM/AML/HCTZ 40/10/0 mg		
846 subjects	630	OM/AML/HCTZ 40/0/25 mg		OM/AML/HCTZ 40/0/25 mg (637 subjects)	
	naïve	7	OM/AML/HCTZ 0/0/0 mg		OM/AML/HCTZ 40/0/25 mg
	naïve	1	OM/AML/HCTZ 0/0/0 mg	OM/AML/HCTZ 40/0/25 mg	OM/AML/HCTZ 40/10/25 mg (209 subjects)*
	naïve	208	OM/AML/HCTZ 40/0/25 mg		
808 subjects	592	OM/AML/HCTZ 0/10/25 mg		OM/AML/HCTZ 0/10/25 mg (600 subjects)	
	naïve	8	OM/AML/HCTZ 0/0/0 mg		OM/AML/HCTZ 0/10/25 mg
	naïve	6	OM/AML/HCTZ 0/0/0 mg	OM/AML/HCTZ 0/10/25 mg	OM/AML/HCTZ 40/10/25 mg (208 subjects)*
	naïve	202	OM/AML/HCTZ 0/10/25 mg		

*In total, the OM 40 mg + AML 10 mg + HCTZ 25 mg treatment group was comprised of 627 subjects, consisting of 210, 209, and 208 subjects from each of the three dual combination assignments at Week 4.

AML = amlodipine; HCTZ = hydrochlorothiazide; OM = olmesartan medoxomil.

Source: Post-text Table 15.1.3

There were a total of 2492 subjects enrolled. The primary metric of efficacy was trough mean seated DBP measured at week 12. The method of assessment of effect was an analysis of covariance with blood pressure at baseline as the covariates and treatment, age group, race group and diabetic status as fixed effects. LOCF values were imputed where such data was missing.

In addition to cuff measurements, 440 subjects consented to ABPM assessments at baseline and at the end of week 12.

With respect to the available measurements, three descriptions of the blood pressure effect are of interest:

- ◆ The overall comparison of pooled triple therapy to the individual two component therapies.
- ◆ The comparison of the two component therapies to the triple therapy group that was derived from corresponding therapies. In this study, there were approximately 590 subjects in the dual therapy and 190 in the individual triple therapy groups. The time of comparison is that of week 4 data to end of treatment data. This comparison reflects the effect of adding the third drug to subjects already taking maximal doses of the other two drugs.
- ◆ Ambulatory data for 440 subjects was also available. This measurement allows an assessment of the performance of the drug on blood pressure during the entire dosing interval. The measurement, however, assesses the effect relative to pre-therapy baseline.

The effect of pooled triple therapies to the two component effect on both diastolic and systolic blood pressure is shown below.

Table 2 Seated DBP and SBP comparing pooled triple therapy cohorts to each of the dual therapies

LS Mean \pm SE	DBP	SBP
OLM/AML/HCTZ versus OLM/AML	-3.8 \pm 0.53	-7.1 \pm 0.87
OLM/AML/HCTZ versus OLM/HCTZ	-4.9 \pm 0.53	-7.4 \pm 0.86
OLM/AML/HCTZ versus AML/HCTZ	-6.7 \pm 0.54	-9.6 \pm 0.88

- ◆ Values include last observation carried forward
- ◆ Within treatment p-value testing for significant change from baseline was obtained from an ANCOVA model with baseline blood pressure as a covariate, and fixed effects of treatment, age group, race group and diabetic status.
- ◆ All treatment comparisons were calculated as OLM/AML/HCTZ minus the dual combination treatment group. Least-square mean differences SEs and 2-sided p-values were obtained from an ANCOVA model with baseline blood pressure as a covariate and fixed effects of treatment, age group, race group and diabetic status.
- ◆ All comparisons based on the above model was highly significant p<0.001

The triple therapy is superior in the magnitude of blood pressure effect for both diastolic and systolic blood pressure than the two drug combination at the inter-dosing interval.

The effect of adding the third component to steady state effects of the dual therapies is shown below. At the time the third component was added each subject was treated for between 2-4 weeks with double therapy. This 2-4 week duration is adequate to define the steady state effect of each of the dual therapies. This metric, therefore mirrors the anticipated use of Tribenzor as add on therapy during steady state effects of dual therapies.

These measured effects are not drastically different from the effect comparing the pooled triple therapy to each of the dual therapy cohorts, but magnitude of the effect is somewhat different. These effects are shown in Table 3 (SeDBP) and Table 4 (SeSBP).

Table 3: Effect of going from dual therapy to triple therapy for SeDBP (weeks 4 to 12).

	OLM \pm AML	OLM \pm AML \pm HCTZ	OLM \pm HCTZ	OLM \pm HCTZ \pm AML	AML \pm HCTZ	AML \pm HCTZ \pm OLM
Week 4	83.9 \pm 9.7	83.3 \pm 8.6	84.6 \pm 11.2	83.5 \pm 10.5	86.6 \pm 9.3	86.2 \pm 9.5
Week 12	83.0 \pm 9.8	77.8 \pm 9.8	83.6 \pm 11.5	78.2 \pm 10.4	85.9 \pm 9.3	79.8 \pm 10.1
Change	-0.9 \pm 8.6	-5.5 \pm 9.5	-1.0 \pm 9.4	-5.3 \pm 9.2	-0.7 \pm 8.0	-6.4 \pm 8.7
LS mean change (CI)	-4.2 (-2.7 to -5.7)		-4.3 (-2.8 to -5.8)		-4.4 (-2.9 to -5.9)	

Values from sponsor's table LS mean change calculated by Fanhui Kong, Ph.D.

Table 4: Effect of going from dual therapy to triple therapy for SeSBP (weeks 4 to 12).

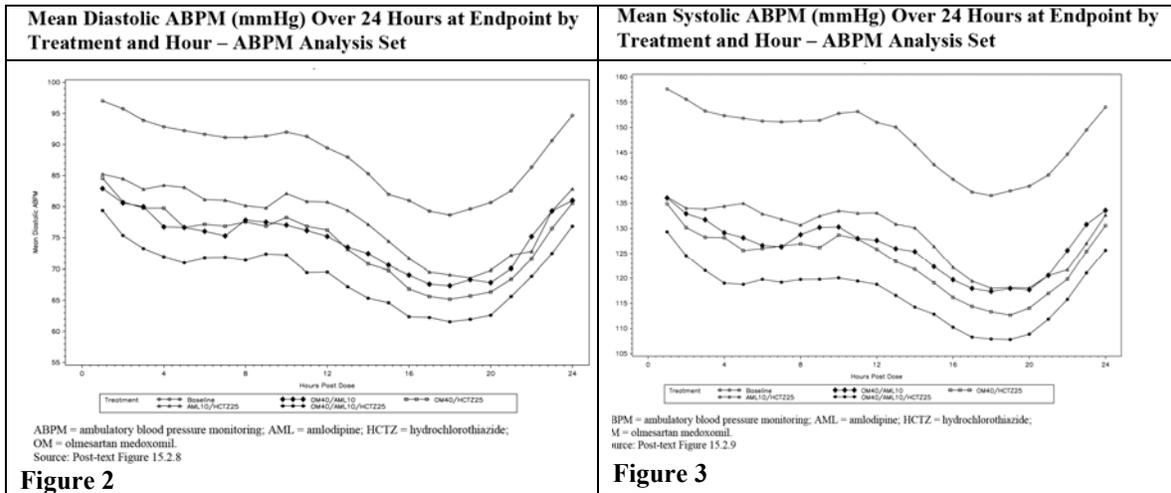
	OLM \pm AML	OLM \pm AML \pm HCTZ	OLM \pm HCTZ	OLM \pm HCTZ \pm AML	AML \pm HCTZ	AML \pm HCTZ \pm OLM
Week 4	138.0 \pm 15.2	137.6 \pm 14.8	139.1 \pm 18.8	136.6 \pm 17.5	140.9 \pm 14.6	141.5 \pm 14.3
Week 12	136.8 \pm 15.4	127.3 \pm 15.5	137.2 \pm 19.4	129.3 \pm 16.9	139.5 \pm 14.4	130.0 \pm 16.3
Change	-1.2 \pm 12.6	-10.3 \pm 14.9	-1.8 \pm 15.7	-7.4 \pm 15.4	-1.5 \pm 12.3	-11.5 \pm 13.4
LS mean change (CI)	-7.7 (-4.9 to -9.6)		-5.2 (-2.9 to -7.6)		-8.5 (-6.0 to -10.7)	

Values from sponsor's table LS mean change calculated by Fanhui Kong, Ph.D.

Ambulatory blood pressure effect:

With respect to the ambulatory data, the measurements were taken at baseline and at end of week 12. There were 440 subjects who had ABPM measurements: 112 treated

with OLM/AML; 116 treated with OLM/ HCTZ; 95 treated with AML/HCTZ; and 117 treated with triple therapy. Although the graphs below do not reflect the drug effect (that would require the change from baseline in each treatment not the comparison from pooled baseline value), the size of the baseline group and the magnitude of diastolic and systolic effects is substantial. The effect on both diastolic and systolic blood pressure appears to persist and is reasonably constant during the dosing interval in each of the dual therapy and triple therapy cohorts. The interdosing interval effect from baseline in SeDBP is approximately 20 mm Hg and for SeSBP approximately 25-30 mm Hg for the triple therapy and somewhat less for each of the dual therapies.



Efficacy by age: The change in SeDBP by pooled triple therapy to the dual therapy regimens did not appear to be dependent on age ≥ 65 and < 65 . The effect with the small number of subjects ≥ 75 (approximately 3% of those enrolled) has a similar magnitude of effect on triple therapy compared to each of the double therapies.

Efficacy by gender: The change in SeDBP by pooled triple therapy was greater than each of the dual therapy regimens for both men and women.

Race: In general the efficacy of the pooled triple therapy for SeDBP was greater than each of the dual therapies for both Black and non-black (largely Caucasian) subjects.

Safety:

Overall disposition

The safety is best also described by two comparisons. The first is the comparison of the pooled data for those treated with pooled triple therapy to each of the double therapy cohorts. In addition, it is reasonable to assess the consequence to the addition of the third component to each of the three dual therapy cohorts. This last analysis requires some knowledge as to the disposition of subjects during the dual therapy portions of the study day 1 to week4 and week 4 to week 12. .

The pooled disposition from day 1 to week 12 is shown in Table 5. The triple therapy group (OLM/AML/HCTZ) includes events which occur prior to the institution of the triple therapy i.e. a subject on one dual therapy during week 3 who discontinues but would have been randomized to triple therapy is included in the triple therapy column.

Table 5-Disposition day 1 to week 12 pooled triple therapy to each double therapy based on week 4-week 12 randomization

	OLM/AML	OLM/HCTZ	AML/HCTZ	OLM/AML/HCTZ
Randomized n=2492	628 (100%)	637 (100%)	600 (100%)	627 (100%)
Completed n=2116	557 (89%)	531 (83%)	512 (85%)	516 (82%)
Discontinued n=376	71 (11%)	106 (17%)	88 (15%)	111 (18%)
Adverse event	22 (4%)	46 (7%)	38 (6%)	48 (8%)
Withdrawal by subject	20 (3%)	21 (3%)	19 (3%)	23 (4%)
Lost to follow-up	15 (2%)	17 (3%)	21 (4%)	26 (4%)
Other	3 (<1%)	9 (1%)	1 (<1%)	6 (1%)
Protocol Violation	11 (2%)	13 (2%)	21 (4%)	8 (1%)
Other meds	0	2 (< 1%)	1 (<1%)	2 (<1%)
Non-compliance	8 (1%)	6 (1%)	6 (1%)	3 (<1%)
Randomization error	2 (< 1%)	3 (< 1%)	1 (< 1%)	3 (< 1%)
Other violations	1 (< 1%)	2 (< 1%)	1 (< 1%)	0
Safety set n=2491	628 (100%)	637 (100%)	600 (100%)	626 (100%)
Safety set 2 n=2302	596 (95%)	580 (91%)	552 (92%)	574 (92%)
ABPM n=440	112 (18%)	116 (18%)	95 (16%)	117 (19%)
<ul style="list-style-type: none"> ◆ Safety set are those with at least 1 dose of study medication and at least 1 post dose safety assessment ◆ Safety set 2 who received at least one dose of medication beyond week 3 ◆ The ABPM set includes 				

There was only a slightly greater percent of subjects who dropped out for adverse event among those randomized to triple therapy than those who were on each of the dual therapies. There were substantially more dropouts in the OLM/HCTZ or AML/HCTZ group than in the OLM/AML group 106, 88 versus 71, respectively during day 1-week 12.

In order to have a better understanding of the process of starting on high doses of dual antihypertensive therapies, the disposition of patients during day 1 to week 4 are shown in Table 6.

Table 6-Disposition day 1 to week 4 based on the dose which was received during the week 1-4 period

	OLM/AML	OLM/HCTZ	AML/HCTZ	PBO
Randomized n=2492	838 (100%)	846 (100%)	808 (100%)	36 (100%)
Completed week 4; n=2303	788 (94%)	772 (91%)	743 (92%)	35 (97%)
Discontinued n=189	50 (6%)	74 (9%)	65 (8%)	1 (3%)
Adverse event	25 (3%)	45 (5%)	31 (4%)	0
Withdrawal by subject	6 (1%)	11 (1%)	15 (2%)	0
Lost to follow-up	10 (1%)	10 (1%)	15 (2%)	1 (3%)
Other	3 (<1%)	1 (<1%)	1 (<1%)	0
Protocol Violation	6 (1%)	7 (1%)	3 (<1%)	0
Other meds	0	1 (< 1%)	0	0
Non-compliance	4 (<1%)	0	0	0
Randomization error	1 (< 1%)	4 (< 1%)	2 (< 1%)	0
Other violations	1 (< 1%)	2 (< 1%)	1 (< 1%)	0

There were a substantially greater percentage of subjects who were allocated during the first 4 weeks to the OLM/HCTZ and AML/HCTZ who discontinued, primarily for adverse events than those allocated to OLM/AML. Note that the numbers of subjects to each of the dual therapies also include those who will eventually be randomized to triple therapy.

The large number of events may potentially be ascribed to the aggressive use of the high dose of dual therapy without an intervening dose titration step.

The disposition of pooled triple therapy to the cohorts of dual therapy treatments during weeks 4-12 is shown in Table 7:

Table 7-Disposition of patients: weeks 4-12 pooled triple therapy

	OLM/AML	OLM/HCTZ	AML/HCTZ	OM/AML/HCTZ
Randomized n=2303	595 (100%)	531 (100%)	552 (100%)	516 (100%)
Completed n=2116	557 (94%)	531 (91%)	512 (93%)	516 (90%)
Discontinued n=187	38 (6%)	50 (9%)	40 (7%)	59 (10%)
Adverse event	7 (1%)	11 (2%)	12 (2%)	23 (4%)
Withdrawal by subject	15 (3%)	15 (3%)	7 (1%)	14 (2%)
Lost to follow-up	8 (1%)	9 (2%)	14 (3%)	13 (2%)
Other	2 (<1%)	8 (1%)	0	4 (1%)
Protocol Violation	6 (1%)	7 (1%)	7 (1%)	5 (1%)
Other meds	0	1 (<1%)	1 (<1%)	2 (<1%)
Non-compliance	5 (1%)	6 (1%)	0	2 (<1%)
Randomization error	1 (<1%)	0	0	0
Other violations	0	0	0	0
<ul style="list-style-type: none"> ◆ Safety set are those with at least 1 dose of study medication and at least 1 post dose safety assessment ◆ Safety set 2 who received at least one dose of medication beyond week 3 ◆ The ABPM set includes ◆ Derived from sponsor's table 15.1.5 				

Considering the week 4-12 was the longer duration of the study, a disproportionate number of subjects discontinued during the week 1-4 stage.

The triple therapy cohort should be broken down by the double therapy group from which they are derived. The disposition of the cohorts based on the dual therapy of origin is shown as Table 8.

Table 8- Disposition of patients: weeks 4 to 12 by week 4 cohort[#].

Week 4 therapy	OLM/AML		AML/HCTZ		OLM/HCTZ	
Week 4-12 therapy	OLM/AML	Triple-HCTZ added	AML/HCTZ	Triple-OLM added	OLM/HCTZ	Triple-AML added
N=	596	192	552	191	580	191
Completed n=2116	557 (94%)	179 (93%)	512 (93%)	164 (86%)	531 (92%)	173 (91%)
Discontinued n=187	39 (7%)	13 (7%)	40 (7%)	27 (14%)	49 (8%)	13 (7%)
Adverse event	7 (1%)	7 (4%)	11 (2%)	9 (5%)	11 (2%)	7 (4%)
Withdrawal by subject	15 (3%)	3 (2%)	8 (1%)	8 (4%)	14 (2%)	3 (2%)
Lost to follow-up	9 (2%)	2 (1%)	14 (3%)	14 (3%)	9 (2%)	2 (1%)
Other	2 (<1%)	1 (1%)	0	2 (1%)	2 (<1%)	1 (1%)
Protocol Violation	6 (1%)	0	7 (1%)	3 (2%)	7 (1%)	2 (1%)
Other meds	0	0	1 (<1%)	1 (1%)	0	1 (1%)
Non-compliance	5 (1%)	0	6 (1%)	1 (1%)	6 (1%)	1 (1%)
Randomization error	1 (<1%)	0	0	1 (1%)	1 (1%)	0
Other violations	0	0	0	0	0	0

Table sent to me by M. Patel of Daiichi Sankyo dated July 12, 2010

[#]There are slight differences between Tables 7 and 8 that for which I don't have an explanation.

There was an excess of percentage of patients listed as discontinuations particularly in the triple therapy group derived from the AML/HCTZ. There were only small differences in the dropout rates those allocated to triple therapy from the other two dual therapies. Adverse events, as a percentage of patients who had events, were greater for the triple therapy groups to each of the dual therapy groups from which the triple therapy cohort was derived.

Specific adverse events:

The specific adverse events will be described both by the day 1 to week 4 period and the week 4 to week 12 periods. The week 4 to week 12 period will be described both by the pooled triple therapy group and by the triple therapy groups as derived from each of the dual therapies.

Adverse events day 1 to week 4: For listed adverse events > 2% in any double therapy group are shown in Table 9:

Table 9: Adverse events (> 2% in any dual therapy group) during day 1 through week 4.

	OLM/AML	OLM/HCTZ	AML/HCTZ	PBO
N=	838	845	807	36
Any treatment emergent adverse event n=978	319 (38%)	328 (39%)	324 (40%)	9 (25%)
Severity				
Mild	191 (23%)	201 (24%)	187 (23%)	6 (17%)
Moderate	111 (13%)	101 (12%)	120 (15%)	2 (6%)
Severe	17 (2%)	<u>26 (3%)</u>	17 (2%)	1 (3%)
Any serious adverse event	4 (< 1%)	10 (1%)	5 (1%)	1 (3%)
Specific systems and adverse events > 2% in any non-placebo group: Underlined numbers are numbers which appear different than other double combinations (no statistical test applied)				
Nervous system disorders	81 (10%)	<u>121 (14%)</u>	79 (10%)	0
Dizziness	33 (4%)	<u>67 (8%)</u>	24 (3%)	0
Headache	40 (5%)	36 (4%)	41 (5%)	0
General disorders and administration site conditions	83 (10%)	<u>61 (7%)</u>	89 (11%)	0
Edema peripheral	43 (5%)	<u>6 (1%)</u>	43 (5%)	0
Fatigue	27 (3%)	34 (4%)	28 (4%)	0
Gastrointestinal disorders	49 (6%)	60 (7%)	68 (8%)	2 (6%)
Nausea	14 (2%)	<u>25 (3%)</u>	19 (2%)	0
Constipation	7 (1%)	7 (1%)	15 (2%)	1 (3%)
Diarrhea	11 (1%)	14 (2%)	5 (1%)	0
Dry mouth	<u>1 (< 1%)</u>	7 (1%)	10 (1%)	0
Musculoskeletal and connective tissue disorders	48 (6%)	37 (4%)	56 (7%)	1 (3%)
Muscle spasm	10 (1%)	15 (2%)	13 (2%)	0
Joint swelling	13 (2%)	<u>1 (< 1%)</u>	16 (2%)	0
Infections and infestations	53 (6%)	41 (5%)	39 (5%)	2 (6%)
Urinary tract infections	12 (1%)	6 (1%)	8 (1%)	1 (3%)
Nasopharyngitis	5 (1%)	9 (1%)	6 (1%)	0
Upper respiratory tract infection	10 (1%)	6 (1%)	2 (< 1%)	1 (3%)
Investigations	25 (3%)	26 (3%)	26 (3%)	2 (6%)
Albumin urine present	6 (1%)	7 (1%)	5 (1%)	1 (3%)
Heart rate increased	1 (< 1%)	6 (1%)	4 (< 1%)	0
Skin and subcutaneous tissue disorders	17 (2%)	26 (3%)	28 (3%)	0
Rash	3 (< 1%)	5 (1%)	10 (1%)	0
Respiratory, thoracic and mediastinal disorders	19 (2%)	28 (3%)	20 (2%)	2 (6%)
Cough	1 (< 1%)	<u>13 (2%)</u>	7 (1%)	0
Renal and urinary disorders	24 (3%)	23 (3%)	19 (2%)	2 (6%)
Pollakuria	9 (1%)	14 (2%)	5 (1%)	1 (3%)
Psychiatric disorders	19 (2%)	17 (2%)	14 (2%)	1 (3%)
Metabolism and nutrition disorders	14 (2%)	13 (2%)	13 (2%)	1 (3%)
Injury, poisoning and procedural complications	13 (2%)	10 (1%)	16 (2%)	0
Vascular disorders	10 (1%)	16 (1%)	6 (1%)	0
Eye disorders	8 (1%)	12 (1%)	10 (1%)	0
Cardiac disorders	5 (1%)	11 (1%)	8 (1%)	0

There were only small differences in the numbers of and severity of adverse events during the first 4 weeks. The most obvious differences were the number of subjects with peripheral edema in the AML cohorts. Dizziness was more common in the OLM/HCTZ cohort.

- ◆ There was a small increase in the number of subjects treated with OLM/HCTZ who had severe adverse events.
- ◆ Nervous system conditions primarily dizziness was increased in the OLM/HCTZ group.

- ◆ Peripheral edema was less in the OLM/HCTZ group.
- ◆ Nausea was more common in the OLM/HCTZ cohort.
- ◆ Dry mouth was less on OML/AML

The specific adverse events, based on the cohort that the triple therapy was derived, are shown in Table 10.

Table 10: Adverse events weeks 4-12 based on treatment at week 4.

Week 4 therapy	AML/HCTZ		OLM/AML		OLM/HCTZ	
Week 4-12 therapy	AML/HCTZ	Triple-OLM added	OLM/AML	Triple-HCTZ added	OLM/HCTZ	Triple-AML added
N=	552	191	596	192	580	191
Any treatment emergent adverse event n=	234 (42%)	72 (38%)	212 (36%)	<u>85 (44%)</u>	214 (37%)	75 (39%)
Severity						
Mild	125 (23%)	41 (22%)	114 (19%)	<u>46 (24%)</u>	116 (20%)	40 (21%)
Moderate	97 (18%)	28 (15%)	85 (14%)	<u>31 (16%)</u>	89 (15%)	28 (15%)
Severe	12 (2%)	3 (2%)	13 (2%)	<u>8 (4%)</u>	9 (2%)	7 (4%)
Any serious adverse event	9 (2%)	5 (3%)	7 (1%)	2 (1%)	5 (1%)	2 (1%)
Specific systems and adverse events > 2% in group: Underlined numbers are numbers which appear different the double combination from which the triple therapy was derived (no statistical test applied).						
Nervous system disorders	29 (5%)	18 (9%)	47 (8%)	<u>30 (16%)</u>	59 (10%)	23 (12%)
Dizziness	8 (1%)	<u>11 (6%)</u>	11 (2%)	<u>17 (9%)</u>	21 (4%)	<u>11 (6%)</u>
Headache	5 (1%)	4 (2%)	20 (3%)	6 (3%)	17 (3%)	5 (3%)
Hypoesthesia	2 (< 1%)	2 (1%)	4 (1%)	1 (1%)	9 (2%)	4 (1%)
Paresthesia	6 (1%)	0	6 (1%)	1 (1%)	6 (1%)	0
General Disorders and Administration Site Conditions	48 (9%)	16 (8%)	50 (8%)	18 (9%)	<u>11 (2%)</u>	23 (12%)
Edema Peripheral	13 (2%)	7 (4%)	22 (4%)	6 (3%)	5 (1%)	<u>14 (7%)</u>
Fatigue	2 (< 1%)	<u>5 (3%)</u>	17 (3%)	5 (3%)	4 (1%)	<u>4 (4%)</u>
Influenza-like illness	2 (< 1%)	2 (1%)	1 (< 1%)	1 (1%)	0	0
Pain	0	0	0	2 (1%)	0	3 (2%)
Gastrointestinal Disorders	30 (5%)	7 (4%)	30 (5%)	10 (5%)	29 (5%)	12 (6%)
Diarrhea	7 (1%)	2 (1%)	7 (1%)	2 (1%)	2 (< 1%)	4 (2%)
Nausea	6 (1%)	0	5 (1%)	3 (2%)	6 (1%)	1 (1%)
Vomiting	6 (1%)	2 (1%)	3 (1%)	1 (1%)	5 (1%)	0
Dry mouth	3 (1%)	2 (1%)	3 (1%)	0	3 (1%)	0
Constipation	5 (1%)	1 (1%)	4 (1%)	1 (1%)	1 (< 1%)	0
Dyspepsia	4 (1%)	0	1 (< 1%)	0	2 (< 1%)	0
Gastritis	2 (< 1%)	2 (1%)	0	1 (1%)	1 (< 1%)	1 (1%)
Musculoskeletal and connective Tissue Disorders	37 (7%)	15 (8%)	41 (7%)	12 (6%)	35 (6%)	11 (6%)
Arthralgia	7 (1%)	3 (2%)	9 (2%)	2 (1%)	8 (1%)	2 (1%)
Back pain	5 (1%)	4 (2%)	7 (1%)	2 (1%)	6 (1%)	1 (1%)
Muscle spasm	3 (1%)	2 (1%)	5 (1%)	5 (3%)	6 (1%)	2 (1%)
Joint swelling	7 (1%)	2 (1%)	7 (1%)	0	2 (1%)	4 (2%)
Pain in extremity	4 (1%)	2 (1%)	3 (1%)	2 (1%)	3 (1%)	0
Infections and infestations	59 (11%)	15 (8%)	63 (11%)	16 (8%)	67 (12%)	15 (8%)
Urinary tract infections	13 (2%)	4 (2%)	21 (4%)	3 (2%)	15 (3%)	3 (2%)
Nasopharyngitis	12 (2%)	3 (2%)	10 (2%)	5 (3%)	15 (3%)	4 (2%)
Sinusitis	7 (1%)	1 (1%)	5 (1%)	5 (3%)	6 (1%)	0
Bronchitis	7 (1%)	0	4 (1%)	1 (1%)	9 (2%)	2 (1%)

Investigations	22 (4%)	9 (5%)	<u>5 (1%)</u>	10 (5%)	13 (2%)	7 (4%)
Blood potassium decreased	<u>13 (2%)</u>	3 (2%)	0	1 (1%)	2 (<1%)	1 (1%)
Blood creatinine increased	3 (1%)	2 (1%)	0	4 (2%)	4 (1%)	2 (1%)
Blood urea increased	1 (<1%)	0	0	3 (2%)	2 (<1%)	2 (1%)
Weight increased	0	2 (1%)	1 (<1%)	1 (1%)	2 (<1%)	1 (1%)
Skin and subcutaneous tissue disorders	13 (2%)	3 (2%)	16 (3%)	8 (4%)	10 (2%)	4 (2%)
Rash	3 (1%)	0	4 (1%)	0	3 (1%)	2 (1%)
Pruritis	1 (<1%)	0	3 (1%)	3 (2%)	0	0
Respiratory, thoracic and mediastinal disorders	28 (5%)	10 (5%)	15 (3%)	3 (2%)	33 (6%)	8 (4%)
Cough	9 (2%)	3 (2%)	5 (1%)	0	8 (1%)	4 (2%)
Pharyngolaryngeal pain	3 (1%)	3 (2%)	0	1 (1%)	8 (1%)	1 (1%)
Dyspnea	6 (1%)	2 (1%)	2 (<1%)	0	3 (1%)	1 (1%)
Nasal congestion	2 (<1%)	0	4 (1%)	1 (1%)	6 (1%)	0
Respiratory tract infection	1 (<1%)	1 (1%)	0	2 (1%)	3 (1%)	0
Renal and urinary disorders	11 (2%)	3 (2%)	7 (1%)	1 (1%)	5 (1%)	4 (2%)
Pollakuria						
Psychiatric Disorders	12 (2%)	3 (2%)	10 (2%)	4 (2%)	4 (1%)	4 (2%)
Anxiety	2 (<1%)	1 (1%)	2 (<1%)	2 (1%)	2 (<1%)	1 (1%)
Metabolism and Nutrition disorders	37 (7%)	3 (2%)	5 (1%)	3 (2%)	11 (2%)	4 (2%)
Hypokalemia	<u>25 (5%)</u>	1 (1%)	0	1 (1%)	2 (<1%)	0
Gout	6 (1%)	0	1 (<1%)	0	1 (<1%)	0
Hyperkalemia	0	1 (1%)	0	2 (1%)	1 (<1%)	0
Injury, Poisoning and Procedural complications	22 (4%)	3 (2%)	15 (3%)	6 (3%)	13 (2%)	1 (1%)
Joint sprain	4 (1%)	1 (1%)	1 (<1%)	2 (1%)	3 (1%)	1 (1%)
Fall	4 (1%)	2 (1%)	0	0	0	0
Vascular disorders	1 (<1%)	<u>4 (2%)</u>	3 (1%)	<u>5 (3%)</u>	7 (1%)	2 (1%)
Hypotension	0	<u>2 (1%)</u>	0	<u>4 (2%)</u>	3 (1%)	2 (1%)
Eye disorders	5 (1%)	0	7 (1%)	3 (2%)	5 (1%)	2 (1%)
Cardiac disorders	1 (<1%)	3 (2%)	10 (2%)	2 (1%)	5 (1%)	2 (2%)
Palpitations	1 (<1%)	2 (1%)	3 (<1%)	1 (1%)	2 (<1%)	0
Ear and labyrinth disorders	3 (1%)	3 (2%)	1 (<1%)	1 (1%)	2 (1%)	4 (2%)
Vertigo	1 (<1%)	2 (1%)	0	1 (1%)	1 (<1%)	0
Neoplasms benign, malignant and unspecified	3 (1%)	0	4 (1%)	2 (1%)	1 (<1%)	2 (1%)

- ◆ Nervous system disorders mostly evidenced by dizziness were more frequent in the triple than in the originating double therapies.
- ◆ Not surprising, when AML is added to OLM/HCTZ, edema increased.
- ◆ There was an increase in fatigue in triple therapy compared to the two dual therapy combinations containing HCTZ.

Vital signs:

In considering the pooled triple therapy groups, there were minimal changes in heart rates from baseline to week 12 (I can't tell the timing of the heart rate measurements relative to dosing). The heart rate change in the triple therapy group was approximately 0.7 BPM above baseline. The heart rate change in the AML/HCTZ was approximately 1 BPM above baseline.

Deaths, Dropouts, Discontinuations and serious adverse events:

There was one death during the study. The event occurred on study day 5 due to ethanol intoxication. The allocated treatment was OLM/AML.

Table 11: Serious adverse events and discontinuations, based on randomized therapy
√-events day 1 to week 4.

Patient ID	Demographics Age (yrs)/Race/Gender	Event(s)	Day of study start or date D/C med	Serious? D/c'd?	Reviewer's comments
Randomized to OLM/AML at week 4: 10 subjects with serious adverse events. 22 subjects discontinued for adverse events.					
0091-0004	43/B/M	Ruptured appendix	32	Yes	
√0112-0044	77/W/F	Pneumonia	26	Yes, d/c'd	
0121-0068	65/B/M	Worsening of osteoarthritis	68	Yes	
		Allergic reaction	68	Yes	
√0125-0020	60/W/F	Gastrointestinal bleed	15	Yes	Received transfusion and D/c'd day 43
0200-0013	63/B/F	Angina	34	Yes, d/c'd	MI ruled out
0313-0009	58/W/M	Acute myocardial infarction and coronary artery disease	31	Yes	CABG performed
√0325-0003	44/B/M	Carcinoma of colon	9	Yes	
0329-0006	58/B/F	Septic knee	36	Yes	No growth but WBC in tap and treated with antibiotics
0334-0010	53/W/M	Right ventricular failure	50	Yes, d/c'd	
		Sleep apnea	51		
0340-0002	72/W/M	Osteoarthritis of shoulder	59	Yes	
0049-0006	54/W/M	Tired and right leg swelling	28	No, d/c'd	
√0070-0051	51/W/F	Vertigo and lightheadedness	4	No, d/c'd	D/c'd on day 18
√0071-0004	71/W/F	Dizziness, low blood pressure and weakness	26	No, d/c'd	
√0090-0002	59/W/M	Bilateral leg edema	12	No, d/c'd	D/c'd day 35
0097-0002	59/B/F	Leg cramping	31	No, d/c'd	
√0112-0032	37/W/M	Edema lower extremities	25	No, d/c'd	
√0128-0074	74/W/M	Worsening hypertension	5	No, d/c'd	BP at time of D/c Not included-previous day 163/91
√0129-0008	48/B/F	Swollen feet	2	No, d/c'd	
√0137-0006	48/W/M	Vertigo and decreased energy	5	No, d/c'd	D/c'd day 15
√0159-0007	37/W/M	Shortness of breath, worsening of pedal edema and fatigue	16-18	No, d/c'd	Right heart failure?
√0159-0019	52/W/M	Fatigue	2	No, d/c'd	Last dose day 11
√0172-0003	48/W/F	Low blood pressure	4	No, d/c'd	Value of BP at time of event unknown
√0204-0003	49/W/F	Dizziness	21	No, d/c'd	BP at event unknown
√0211-0006	48/W/F	Chest pressure	2	No, d/c'd	No work-up stated
0220-0012	43/W/M	Worse hypertension	56	No, d/c'd	BP 163/100
0241-0005	48/W/M	Bilateral lower extremity edema	72	No, d/c'd	Completed study but did not enter open-label study
√0264-0004	73/W/M	Fatigue	3	No, d/c'd	D/c'd day 26
0279-0011	64/W/M	Hypotension	7-22	No, d/c'd	BP several times systolic < 100, DBP 44-63
0282-0002	75/W/M	Dizziness	72	No, d/c'd	BP at event not known
OLM/HCTZ 14 subjects with serious adverse events; 47 patients discontinued for adverse events					
√0015-0021	54/W/M	Chest pain, shortness of breath and diaphoresis- coronary artery spasm	26	Yes, d/c'd	Catheterization showed normal coronary arteries
0035-0018	77/W/M	Acute cerebellar infarction	42	Yes d/c	Last BP was 149/78

√0065-0012	41/W/M	Non cardiac chest pain	15	Yes d/c	No evidence of MI by enzymes or ECG
√0076-0005	53/W/F	Cerebro-vascular accident	27	Yes	
0091-0001	47/W/F	Ovarian cyst	81	Yes	
√0147-0036	70/W/F	Chest pain	14	Yes	Diagnosed as musculo-skeletal
√0156-0025	35/A/F	Chest pain	5	Yes, d/c'd	Work-up negative for myocardial infarction and pulmonary embolism
√0184-0001	54/W/F	Chest pain and worse HBP	16	Yes, d/c'd	
0233-002	63/W/M	Bladder cancer	72	Yes	
√0248-0037	25/W/M	Adrenal adenoma; Hyperkalemia and acute renal failure	5 12	Yes, d/c'd	K+ = 2.8; baseline was 3.1; stopped medication; creatinine day 12 was 2.02; K+ =6.7
0257-0007	41/B/M	Cerebro-vascular accident	82	Yes, d/c'd	
√0350-0004	56/W/M	Acute myocardial infarction	3	Yes, d/c'd	Catheterized
0356-001	57/W/M	Worsening diabetes	56	Yes	Hospitalized
√0015-0021	63/W/M	Dizziness, light headed shortness of breath, fatigue, hypotension and blurred vision	5	No, d/c'd	
√0021-0017	53/W/M	Decrease in BP	3	No, d/c'd	Day 5 BP 102/73-D/c'd day 5
√0041-0017	64/W/M	Dizziness, fatigue worse headache, nausea and blurred vision	3-10	No, d/c'd	No clear work-up supplied, symptoms eventually resolved
√0045-0032	46/W/M	Hypotension	3	No, d/c'd	BP not captured
√0051-0029	56/B/M	Presyncope	4	No, d/c'd	
0052-0016	61/W/M	Hypotension	82	No, d/c'd	BP not captured
√0052-0022	52/B/F	Dizziness	3	No, d/c'd	BP not captured
0053-0004	70/B/F	Bruises on legs, dizziness, ankle swelling, lethargy and fogginess in eye	43	No, d/c'd	D/c'd study day 65.
√0062-0011	63/W/M	Syncopal episode	10	No, d/c'd	
√0080-0009	56/B/M	Urticaria	22	No, d/c'd	
√0100-0030	60/W/M	Itching	1	No, d/c'd	
0111-0074	50/B/M	Shortness of breath	62	No, d/c'd	Work-up not stated
√0112-0038	62/W/F	Dizziness and hypotension	5	No, d/c'd	D/c day 15
√0121-0005	59/W/F	Dizziness, nausea and palpitations	5	No, d/c'd	ECG not stated
0122-0024	61/B/F	Numbness and tingling left arm and side of mouth;	28-34	No, d/c'd	Work-up unclear
0141-0023	53/B/M	Cardiac chest pain and shortness of breath	78	No, d/c'd	Completed double blind study did not enter OL study
0143-0006	53/B/M	Difficulty swallowing, fatigue and sore throat	59	No, d/c'd	
√0155-0024	71/W/M	Decreased energy	27	No, d/c'd	
0158-0016	49/B/F	Hair loss	62	No, d/c'd	
√0159-0021	49/W/M	Disorientation, dizzy, nausea and sore nipples	4	No, d/c'd	D/c'd day 14
√0163-0013	60/W/M	Symptomatic hypotension	10	No, d/c'd	BP 96/64
√0172-0002	51/B/F	Headache	15	No, d/c'd	D/c'd day 28
√0176-0015	65/B/F	Headaches and body aches	5	No, d/c'd	D/c'd day 8
√0196-0026	26/W/F	Dizziness and worsening headaches	3	No, d/c'd	D/c'd day 18
√0201-0002	41/W/M	Chest pain	4	No, d/c'd	Work-up not stated
√0202-0007	65/W/F	Mild dizziness and feeling of increased pulse	1	No, d/c'd	Work-up not stated
√0208-0006	61/W/M	Dizziness and hypotension	5	No, d/c'd	BP 80/40- D/c'd day 9

√0223-00016	69/W/F	Rash	10	No, d/c'd	
0223-0029	71/W/M	Dizziness, lightheadedness and hypotension	30	No, d/c'd	BP day before event was 140/76; BP at event not stated.
√0230-0015	62/W/F	Hypotension	14	No, d/c'd	BP not stated
0237-0006	37/W/M	Elevated creatinine and BUN	42	No, d/c'd	Cr increased to 2.35 from 1.21 mg/dL, resolved to 1.34 mg/dL
√0251-0003	55/W/F	Lightheadedness	2	No, d/c'd	D/c'd day 6
0264-0005	60/W/M	Cramping of hands	61	No, d/c'd	
√0302-0009	68/B/F	Headache	4	No, d/c'd	
√0311-0004	80/W/M	Constipation, diarrhea, hemorrhoids, nausea and non-cardiac chest pain	4-6	No, d/c'd	
√0314-0003	54/W/M	Dizziness and lightheadedness	8	No, d/c'd	D/c'd day 11
√0316-0001	58/B/F	Syncopal episode	3	No, d/c'd	Work-up unclear
√0330-0008	43/W/M	Weakness and vertigo	6	No, d/c'd	D/c'd day 30
√0336-0005	33/W/M	Hypotension	4	No, d/c'd	BP unknown
AML/HCTZ 13 subjects with serious adverse events; 34 discontinued for adverse events					
0052-0015	63/W/M	Worsening hiatal hernia, vomiting, hypokalemia	36	Yes	hospitalized
0065-0005	71/W/F	Fall and right hip fracture	36	Yes, d/c'd	
0085-0010	41/W/F	Non-cardiac chest pain	82	Yes	Cardiac work-up was negative PFT shows marked decrease in FEV1/FVC.
0093-0021	69/W/F	Facial cellulitis	51	Yes	After cyst removal from cheek. Hospitalized
√0111-0666	49/B/M	Renal cell carcinoma	14	Yes	Continued post-nephrectomy
√0128-0023	63/B/F	Ataxic gait and left hemiparesis	13	Yes	Work-up ruled out CVA, MS and malignancy. She was treated with platelet inhibitors and anticoagulants
0156-0013	38/W/M	Fracture of bone in hand		Yes	Can't find reference that was cited in primary medical/statistical review.
√0173-0011	61/W/M	Fall and acute fracture	13	Yes, d/c'd	Fell from roof. BP 138/64
0196-0017	48/B/F	Fall, acute renal failure and syncope	33	Yes, d/c'd	Had low BP on admission. Renal function results Not stated.
0208-0016	67/W/M	Right lower lobe community acquired pneumonia	52	Yes	
√0295-0003	49/W/F	Hypertensive urgency, atypical chest pain	2	Yes, d/c'd	The BP for which the hypertensive urgency was diagnosed was not stated.
0297-0001	64/W/M	Prostate cancer	42	Yes	
0316-0027	51/W/F	Hydronephrosis, hypokalemia, hyponatremia, pyelonephritis and sepsis	80	Yes	Went to ER because of motor vehicle accident. BUN was 32 mg/dl and creatinine was 2.0 mg/dL. D/c'd from hospital with BUN=7 mg/dL and creatinine 0.9 mg/dL
√0009-0007	56/W/F	Swelling of both feet	8	No, d/c'd	
√0010-0006	58/W/F	Swelling to knees	14	No, d/c'd	Insufficient information on etiology

√0015-0008	51/W/F	Heart rate increased	18	No, d/c'd	
0025-0015	78/W/F	Significant blood pressure drop	36	No, d/c'd	Systolic < 90 mm Hg
0060-0006	65/W/M	Elevated glucose	57	No, d/c'd	Glucose was 230 mg/dL
√0070-0085	64/W/F	Increased heart rate and restlessness	2	No, d/c'd	Heart rate was 106 BPM
√0070-0195	71/W/M	Constipation	26	No, d/c'd	
√0074-0002	57/W/F	Rapid heart rate	6	No, d/c'd	Heart rate 166. ECG not supplied
√0120-0010	64/W/M	Worsening hypokalemia	1	No, d/c'd	K += 2.9 mmol/L
√0122-0025	55/W/M	Edema bilateral feet and ankles	13	No, d/c'd	
√0142-0015	49/B/F	Shivers, increased depression, lightheaded, epistaxis, fatigue and facial rash	2-15	No, d/c'd	
√0147-0028	71/W/F	Bilateral pedal edema	20	No, d/c'd	
√0152-0003	70/B/F	Edema of ankles	5	No, d/c'd	
√0154-0015	45/W/F/	Cough	5	No, d/c'd	
√0162-0003	52/W/F/	Headache	2	No, d/c'd	
√0165-0010	38/W/M	Exacerbation of migraines and nausea	3	No, d/c'd	
√0177-0006	45/B/M	Chest pressure (mild), lightheadedness, shortness of breath (mild) and arm tingling	2	No, d/c'd	
√0180-0006	67/W/M	Bilateral edema of ankles and feet	18	No, d/c'd	
√0181-0022	62/W/F	Bilateral pitting edema	14	No, d/c'd	
0184-0012	38/W/M	Pneumonia	29	No, d/c'd	
0200-0008	64/W/M	Delayed hypersensitivity reaction	59	No, d/c'd	
√0205-0008	42/W/M	Edema legs	19	No, d/c'd	
√0241-0001	56/W/F	Edema legs, feet and hands	17	No, d/c'd	
√0241-0012	38/W/F	Headaches, swelling bilateral lower extremities and rash on lower extremities	7-9	No, d/c'd	
√0263-0002	62/W/F	Edema of feet	8	No, d/c'd	
√0275-0021	54/W/M	Worsening hypokalemia	16-31	No, d/c'd	K+ baseline was 3.8 mmol/L dropped to 3.0-3.0 mmol/L
0302-0002	61/W/M	Renal insufficiency	89-103	No, d/c'd	Creatinine increased to 3.66 mg/dL from baseline value of 2.44 mg/dL
√0306-0002	58/W/F	Hypotension	3	No, d/c'd	BP unknown
√0313-0013	56/W/F	Hyperemia, worsening of edema and leg pain	23	No, d/c'd	Event on day 30
0323-0018	65/W/F	Right upper extremity paresthesia	63	No, d/c'd	Ongoing work-up Not stated
Triple Therapy 13 with serious adverse events; 46 others discontinued for adverse events					
√0070-0190	50/B/F	Vaginal bleeding due to uterine fibroids	12	Yes, d/c'd	OLM/HCTZ at time of event
0071-0017	70/W/M	Prostate cancer	43	Yes	
0102-0020	66/W/M	Worsening coronary artery disease	82	Yes, d/c'd	Had angioplasty
0111-0041	54/B/M	Right femur osteomyelitis and right foot drop	56	Yes	Hospitalized for treatment of osteomyelitis then developed foot drop.
√0111-0071	53/B/M	Worsening diabetes mellitus	7	Yes, d/c'd	Started on OLM/HCTZ during day 1 to week 4
√0125-0024	45/W/F	Exacerbation of bipolar disorder and crack cocaine dependence	22	Yes, d/c'd	
0150-0009	61/W/F	Shortness of breath and pulmonary atresia	42	Yes	
0152-0032	54/B/M	Restricted airway disease and	72	Yes	BP 164/100 repeated

		syncope			124/78
0204-0015	50/W/M	Pre-renal azotemia	69	Yes	Creatinine 2.5 mg/dL BUN 52. At D/c from hospital creatinine=0.7 mg/dL
0224-0013	70/W/M	Prostate cancer	5	Yes	
0336-0024	65/W/M	Worsening degenerative disc disease	27	Yes	
0343-0023	65/W/M	Severe duodinitis gastritis and rectal bleeding	73	Yes	
0354-0013	67/W/F	Worsening coronary artery disease and non-cardiac chest pain	34	Yes	Catheterized and stented. No evidence of MI.
0015-0009	54/W/M	Ankle edema	20	No, d/c'd	On AML/HCTZ at time of event
0015-0024	54/W/F	Lightheadedness, heart pounding harder and increased urinary frequency	2	No, d/c'd	On OLM/HCTZ at time of event
0016-0004	55/W/F	Cough, dizziness and nausea	14	No, d/c'd	BP closest was 159/102
0018-0019	63/W/F	Anxious, elevated creatinine kinase, low potassium, burning sensation, lightheaded, dry mouth, flushing and loss of consciousness	32	No, d/c'd	Taken to ER values and work-up was not stated. Treated with IV K+.
0039-0006	52/W/F	Dizziness and headache	72	No, d/c'd	BP at time of event was not stated.
0052-0013	60/B/F	Bilateral edema and petechia related to edema	22	No, d/c'd	On OLM/AML at time of event
0073-0012	42/W/F	Symptomatic hypotension	66	No, d/c'd	BP 88/61 at time of event
0088-0002	59/W/F	Hypotension	31	No, d/c'd	BP at event Not known. Next visit BP 100/60
0095-0001	42/W/M	Exacerbation of fatigue, irritability and myalgias	8-12	No, d/c'd	OLM/AML at time of event
0110-0018	66/W/M	Dry cough	8	No, d/c'd	On OLM/HCTZ
0112-0019	45/W/F	Diarrhea, dizziness and headache	20	No, d/c'd	On OLM/AML
0112-0022	61/B/F	Hypotension	2-4	No, d/c'd	On OLM/HCTZ
0126-0007	56/A/M	Dizziness	57	No, d/c'd	BP at time of event unknown previous BP 117/71
0145-0006	59/W/F	Shortness of breath, facial edema and lower extremity edema	23	No, d/c'd	On OLM/AML
0155-0016	66/W/F	Worsening edema of lower extremities	31	No, d/c'd	
0156-0008	62/A/F	Lightheadedness and headache	5	No, d/c'd	On AML/HCTZ at time of event
0159-0015	43/B/F	Uncontrolled hypertension, hypoxemia and SLE worsening	3	No, d/c'd	On OLM/AML
0164-0013	61/W/F	Pedal edema and weight gain	46	No, d/c'd	
0164-0024	30/W/F	Palpitations	58	No, d/c'd	Next day pulse was 98, No ECG
0166-0026	57/W/F	Decreased blood pressure	71	No, d/c'd	Mean BP 98/68
0176-0010	57/B/M	Abdominal cramps, lack of energy, poor appetite, disorientation, dizziness and headaches	42	No, d/c'd	Symptoms of dizziness began while on AML/HCTZ
0183-0021	55/W/M	Increased creatinine and increased BUN	48	No, d/c'd	Baseline Creatinine 1.18 mg/dL at termination 1.52 mg/dL
0183-0023	70/W/F	Hypotension	28	No, d/c'd	Can't tell what treatment subject was on

					at time of hypotension
0183-0031	67/W/M	Frequent premature beats	43	No, d/c'd	Pulse was 36 BPM
√0192-0020	65/W/F	Dizziness excessive fatigue and bilateral ankle edema	9-12	No, d/c'd	On OLM/AML
<u>0202-0001</u>	<u>61/B/M</u>	<u>Elevated creatinine and BUN</u>	<u>43-56</u>	<u>No, d/c'd</u>	<u>Max Cr was 2.37 mg/dL Baseline was 1.46 mg/dL Last off therapy was 1.93 mg/dL (about 20 days after D/c)</u>
0214-0008	53/W/F	Constipation and swelling of lower extremities	34	No, d/c'd	
√0216-0017	47/W/M	Dizziness, lightheaded, SOB , rapid pulse and night sweats	3	No, d/c'd	On OLM/HCTZ
√0220-0002	42/W/F	Bilateral lower leg swelling	6	No, d/c'd	On OLM/AML
<u>0228-0010</u>	<u>48/B/M</u>	<u>Hyperkalemia</u>	<u>44</u>	<u>No, d/c'd</u>	<u>K+= 6.2 mmol/L</u>
0237-0007	63/W/M	Dizziness and headache	42-25	No, d/c'd	BP in that time was 91/65
√0251-0010	57/W/F	Vertigo	10	No, d/c'd	On OLM/HCTZ
<u>0257-0020</u>	<u>61/B/M</u>	<u>Increased serum creatinine and BUN</u>	<u>43</u>	<u>No, d/c'd</u>	<u>Baseline creatinine/ BUN was 1.63/36 mg/dL; last on therapy 2.09 / 43 mg/dL; 34 days later Cr 1.93/30 mg/dL</u>
√0259-0006	86/W/F	Exacerbated lower extremity edema	4	No, d/c'd	On OLM/AML
√0260-0015	27/W/M	Bilateral shoulder an neck pain	18	No, d/c'd	
√0275-0019	54/B/F	Possible seizure	2	No, d/c'd	On OLM/AML
0312-0008	41/B/M	Headache	31	No, d/c'd	
√0316-0123	40/B/M	Shortness of breath	2	No, d/c'd	On OLM/HCTZ
0318-0046	56/B/F	Dizzy, fatigue and hypotension	32	No, d/c'd	BP unknown
√0322-0004	57/W/M	Recurrence in mood swings	1	No, d/c'd	On AML/HCTZ at time of event
√0322-0012	68/W/M	Fatigue and rapid heart rate	3	No, d/c'd	On OLM/HCTZ at time of event
0331-0032	71/W/M	Swelling lower legs and rash	38	No, d/c'd	
√0340-0013	62/W/M	Worsening of fibromyalgia	12	No, d/c'd	
√= subjects with AE < day 28. Bold- hypotensive events after day 28 Underlined- Renal disease or hyperkalemia after day 28.					

Table 12: Some interest events post day 28

Dose	#D/C after day 28	# serious adverse events after day 28	# renal disease or hyperkalemia after day 28	# hypotension/vasodilatation after day 28
OLM/AML	8	7	0	2
AML/HCTZ	8	9	4	3
OLM/HCTZ	12	5	2	1
Triple	22	8	6	11

There were more subjects who discontinued after day 28 of therapy among those treated with triple therapy. The number of subjects with serious adverse events after day 28 shows only a weak signal. Overall there was a small increase in the number of subjects with either hyperkalemia or renal dysfunction after day 28 and an increase in vasodilatation/hypotension in the triple therapy group after day 28.

Laboratory:

Selected laboratory parameters and the change from baseline during the double-blind portion of the trial are shown below.

Change from baseline mean (SD)

Parameter	OLM/AML	OLM/HCTZ	AML/HCTZ	Triple
Hematology				
Hemoglobin g/dL	-0.3 ± 0.8	-0.2 ± 0.9	0.0 ± 0.7	-0.5 ± 0.85
Hematocrit %	-1.4 ± 2.6	-1.5 ± 2.7	-0.7 ± 2.4	-2.3 ± 2.8
Platelets 10 ³ /μL	10.5 ± 37	2.9 ± 32	18.7 ± 38	13.5 ± 30
WBC count 10 ³ /μL	0.07 ± 1.4	0.14 ± 1.4	0.39 ± 1.2	0.3 ± 1.5
Chemistry				
BUN mg/dL	0.8 ± 3.9	3.5 ± 5.0	1.2 ± 4.4	3.4 ± 5.2
Creatinine mg/dL	-0.03 ± 0.2	0.07 ± 0.2	0.01 ± 0.2	0.06 ± 0.2
Sodium mmol/L	0.2 ± 2.4	-0.2 ± 2.9	0.1 ± 2.6	-0.3 ± 2.6
Potassium mmol/L	0.09 ± 0.4	-0.03 ± 0.4	-0.33 ± 0.4	-0.04 ± 0.4

The effect of triple therapy appears to be no worse than the effect of one of the two-drug combinations.

Appendix A
DMEPA's comments:

3.1.1 General Comments

1. The established name as presented lacks the word “and.” We recommend revising to read “Olmesartan Medoximil, Amlodipine, and Hydrochlorothiazide.”
2. The presentation of the strength throughout the labeling requires the unit of measure (mg) for all active ingredients to be consistent with the presentation on the container labels and carton labeling. The strength should be presented as 20 mg/5 mg/12.5 mg, 40 mg/5 mg/12.5 mg, 40 mg/5 mg/25 mg, 40 mg/10 mg/12.5 mg, and 40 mg/10 mg/25 mg.

3.1.2 Insert Labeling – Full Prescribing Information

3.1.2.1 Section 2 Dosage and Administration

The language for dosing of Tribenzor in replacement therapy is inconsistent between the Highlights section and the Full Prescribing Information. The statement for Replacement Therapy in Full Prescribing Information Section 2 reads, (b) (4)

(b) (4)

(b) (4) The Highlights section states “Dosage may be increased..... usually by increasing one component at a time...” Therefore, to be consistent with the Highlight section, we recommend that the statement in the Dosage and Administration section be revised to (b) (4)

(b) (4)

3.2 COMMENTS TO THE APPLICANT

A. General Comments – for all container labels and carton labeling

1. Revise the presentation of the established name on the container labels and carton labeling so that it shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features, per 21 CFR 201.10(g)(2).
2. Remove the (b) (4) between the proprietary name and the established name as “the ingredient information required by section 502(e) of the Federal Food, Drug, and Cosmetic Act shall appear together, without any intervening written, printed, or graphic matter...” per 21 CFR 201.10(a).
3. Relocate the dosage form to appear after the active ingredient and before the presentation of the strength on professional sample blisters, container labels, and carton labeling. This is the customary presentation of information and provides for the ease of locating necessary information by healthcare providers and patients. For example:

Tradenname
(Olmesartan Medoximil, Amlodipine, and Hydrochlorothiazide) Tablets
20 mg/5 mg*/12.5 mg
*each tablet contains 6.9 mg amlodipine besylate

B. Carton Labeling and Container Labels for 40 mg/10 mg/25 mg tablets

1. The color utilized to differentiate the 40 mg/10 mg/25 mg tablets (b) (4)
(b) (4)
(b) (4) of the carton labeling and professional

sample blister cards, thus making the strengths more difficult to distinguish. Revised the color used for the presentation of the 40 mg/10 mg/25 mg strength to one not used in the product's trade dress yet still distinguishable from the colors used for the remaining strengths of this product.

- C. Container labels (30 count bottle and seven day sample bottle)
1. As this is unit of use packaging, use child resistance closures to ensure compliance with the Poison Prevention Act.
- D. Container labels (90 count bottle)
1. See Comment C1.
 2. The (b) (4) is inappropriately applied. As presented, the use of the (b) (4) (b) (4) (b) (4) compared to the established name. Remove the (b) (4) (b) (4) After removing the (b) (4) relocate the net quantity to the edge of the principle display panel similar to the net quantity presentation on the 30 count bottle and seven day sample bottle container labels.
- E. Carton Labeling (Hospital Unit-dose 10x10 blister)
1. The prominence of (b) (4) (b) (4) (b) (4) Remove this prominent field to improve the ability of users to better distinguish the product strengths.
- F. Unit Dose Blister (cards of 10 tablets)
1. Revise the presentation of the information to be consistent with Comment A3 but not to include the statement describing the specific amount of salt for amlodipine besylate.
 2. Remove the strengths from the presentation of the established name as this is redundant information on a small label with limited space.
 3. Revise and provide additional methods to distinguish the strengths 20 mg/5 mg/12.5 mg, 40 mg/10 mg/12.5 mg, and 40 mg/5 mg/25 mg. The small font size on the unit dose blister in combination with color fonts used makes it difficult to distinguish these strengths and increases the likelihood of these strengths being confused. Additional distinguishing methods (i.e., highlighting, boxing, outlining, color bars, etc) should be incorporated into these labels.
- G. Professional Sample Carton Labeling
1. Remove the prominent (b) (4) per Comment E1.
- H. Professional Sample Blister (cards of seven tablets)
1. Add the statement "Each tablet contains" to the back of the blister card to include all three active ingredients and their respective strengths. In

addition, place this information so that it will be legible after tablets have been removed.

2. Remove the statement “Tradename 7-Day Sample” as this information detracts from the prominence of the product information on the principle display panel and is redundant.
 3. Remove the prominent purple field per Comment E1.
- I. Alternate Sample Blister (card of seven tablets)
1. Include a statement “Each tablet contains” which describes all the three active ingredients and their respective strengths.

Appendix B CMC comments.

III. List Of Deficiencies To Be Communicated

1. P.2.2.1 Formulation Development:

Provide details of the experimental design and statistical analysis you employed on the 40/10/25 mg strength tablets in investigating the concentration of the (b) (4), pregelatinized starch and croscarmellose sodium. The details should include the polynomial model used, the regression coefficients for main and interacting independent variables, the standard error, the statistical method to determine significance [statistical criteria for goodness of fit of model (R²) and p and t-values to determine the significance of the regression coefficients].

2. P.5.1 Specification

a. Provide a single consolidated drug product specification table that includes release and stability limits.

b. Regarding the Degradation Products test in your specification, the unspecified peak amount is attributed to which drug substance? Additionally, provide a justification for the high acceptance criterion of unidentified total on stability (NMT (b) (4)), considering that actual levels on stability are (b) (4).

c. Regarding the microbial contamination test, you state in P.5.6, 'Justification of Specification' that the frequency of release testing is consistent with the principles of the Periodic Quality Indicator Test (PQIT) program. Accordingly, this test should not be a part of the drug product specification but as a separate "PQIT" test.

3. P.8.2 Postapproval Stability Protocol and Stability Commitment

Your (b) (4) is not acceptable, (b) (4). Accordingly, each stability batch in your plan should conform to the testing frequency stated in ICH Q1A(R2) 2.2.6. – “- the frequency of testing at the long term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed re-test period”. Further, the test for microbial contamination should also be performed at the 12 month time point.

4. Review of Common Technical Document-Quality (Ctd-Q) Module

1A. Labeling& Package Insert

The established names on the container label should be in parenthesis, with the word 'tablets' inserted after the parenthesis.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200175	ORIG-1	DAIICHI SANKYO INC	CS-8635 Combination of olmesartan medoxomil/amlodipine/hydrochlor othiazide

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ABRAHAM M KARKOWSKY
07/15/2010