# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**200045Orig1s000**

# 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: December 8, 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 Amturnide® (NDA 200045, combination product of Aliskiren, Amlodipine and Hydrochlorothiazide; Novartis)

Amturnide® is the combination product for the following three drugs: Amlodipine (AML), Hydrochlorothiazide (HCTZ) and Aliskiren (ALI). All three drugs are currently approved for the treatment of hypertension. Of the three potential dual-therapies (ALI/HCTZ; AML/HCTZ; and ALI/AML) two combinations ALI/HCTZ and ALI/AML are currently approved for the treatment of hypertension.

The result of the primary efficacy study #SAH 2302 for this NDA clearly demonstrates that the three drug combination has a greater systolic blood pressure-lowering effect that any of the three two-drug combinations.

The proposed marketing strengths for the triple combination are shown as Table 1.

**Table 1 Proposed marketing formulations for Amturnide**

| | ALI | AML | HCTZ |
|---|---|---|---|
| Strength 1 | 150 | 5 | 12.5 |
| Strength 2 | 300 | 5 | 12.5 |
| Strength 3 | 300 | 5 | 25 |
| Strength 4 | 300 | 10 | 12.5 |
| Strength 5 | 300 | 10 | 25 |

Currently, there is one outstanding issue, the approval status of one of the manufacturing sites (b) (4).

The major labeling issue is related to an extremely large food effect for ALI. The concentrations of ALI when taken fasted are approximately 8-fold ($C_{max}$) or 5-fold

($AUC_{0-\infty}$) greater than when ALI is taken with high-fat meal. The concentrations at trough for ALI fasted are still substantially greater than to high-fat fed values by approximately a factor of 4. It is currently unclear if the food effect of ALI is limited to a high fat meal. If the effect was limited to the administration of ALI with a high fat meal, since most individuals do not consume a high fat meal at breakfast, the worst case scenario would be easier to label. It is also unclear if the blood pressure effect of ALI is markedly altered by the effects of food.

There are currently several different approved formulations of ALI either as monotherapy or as combination therapy with other anti-hypertensive drugs. Any decision as to how the large food effect will impinge on labeling will also effect these products. I have not edited the label for Amturnide® with recommendations regarding food and the label is similar to the other approved ALI formulations.

My preference for the Amturnide® label and the label of these ALI containing drug or combination products would be to recommend that these formulations be taken fasting for some period of time, prior to altering the dose or adding an additional antihypertensive therapy. The easiest way to assure not taking ALI with food is to recommend that it be taken at night.

The pharmacodynamic consequence of this large food effect is unclear. Optimally, this information could best be determined by a direct comparison of blood pressure effects in groups treated with ALI fed versus ALI fasted. This assessment of the consequence of food on blood pressure may be determined with ALI as monotherapy and not necessarily mandating that each of the combination therapy products be assessed for the food effect on blood pressure.

The sponsor has submitted two studies to the Tekturna® NDA (NDA # 21-985), yet to be reviewed. The first study is the consequence of meals, other than a high fat meal on the pharmacokinetic profile of ALI monotherapy. The second study is the relationship of food on the blood pressure effect of ALI monotherapy. When these studies are fully reviewed, the results might alter the DOSING AND ADMINISTRATION section of more than the monotherapy label.

The relationship between the large food effect and an estimate of the consequence on the dynamic effect on blood pressure will be discussed at the end of the clinical pharmacology section.

The magnitude of effect with triple therapy compared to dual therapy indicates that the third component further decreases blood pressure as assessed either by cuff or ABPM measurements compared to any of the dual therapies. Amturnide® is therefore approvable for the treatment of hypertension pending an acceptable manufacturing site inspection. The population for whom the drug would be recommended in labeling would mirror the labeling of other triple combination therapies which have recently been approved.

This memo relied upon the following reviews:

- Memo by Sudharshan Hariharan, Ph.D., Office of Clinical Pharmacology dated November 24, 2010.
- Memo by Donghao (Robert) Lu, Ph.D., Division of New Drug Quality Assessment October 20-22, 2010.
- Memo by Tien-Mien Chen, Ph.D., ONDQA review dated November 2, 2010.
- Memo by Felicia Duffy, RN, BSN, MSEd, safety evaluator dated May 13, 2010.
- Denial of Proprietary name by Carol A. Holquist, RPh., dated May 19, 2010
- Memo by G. Jagadeesh, Ph.D., Pharmacology/Toxicology Review dated July 28, 2010.
- Review, joint Tsvi Aranoff, M.D. (clinical), and Fanhui Kong, Ph.D. (statistical), dated November 23, 2010.
- Memo by Raanan A. Bloom, Ph.D., for environmental assessment dated December 8, 2010.

Trade-name:

DMEPA considered the TRADENAME Amturnide® acceptable. A final memo from DMEPA is pending.

Environmental assessment (EA):

The EA found no significant impact.

Integrity of data:

The primary efficacy study (#SAH 2302) was carried out in 12 countries and 181 study sites. Approximately 26% of the study sites were in the USA and an additional 25% were in Germany. Only two investigators are listed as having received consulting fees from Novartis of a significant amount. (b) (6) Given the numbers of and distribution of patients in the study, it is unlikely that the results from the sites where the investigators received consulting fees altered the study's results.

Since there were 181 sites and none of the sites appeared to drive the results of the study, the Agency did not request a DSI audit of any sites. The EMEA, however, informed the Agency of deviations from the protocol in the three sites, two sites in Canada and one site in Latvia which they inspected. The deviations consisted of deviations from the stipulated assessment of blood pressure measurements. The protocol required that should one of three values of the systolic blood pressure assessment deviate by more than 10 mmHg from the other two measurements, a second set was to be performed. If any measurement during the second set of triplicate measurements still differed by 10 mmHg, that set of measurements would nevertheless, be accepted. There were in addition, a large number of included subjects who despite having protocol deviations were nevertheless, enrolled. The inspected sites did not perform the second set of measurements in subjects even if the initial set was not acceptable.

None of these deviations appears to introduce bias into the results. If anything, the inclusion of the effects from the subjects with protocol deviations increases the noise of

the study and would make the likelihood of finding a signal more difficult. Consequently, neither the consulting fees nor the deviations from the protocol were sufficient to compromise the results of the study.

CMC:

The product is a film coated tablet containing the three active components. The CMC reviewer considered the application as approvable pending the clearance by compliance of one site (b) (4).

The expiration date recommended by the CMC reviewer was 24 months for the bottle packaging and 18 months for the blister packaging.

Pharmacology/Toxicology:

There were no pharmacology or toxicology studies submitted for review. Dr. Jagadeesh edited the proposed labeling.

Clinical Pharmacology:

There appears to be a pharmacokinetic interaction between the three components of the combination triple therapy when it is studied at less than the maximum dose of the triple therapy i.e. ALI 300/ AML 5/HCTZ 25 (and not ALI 300/AML10/HCTZ 25, study #CSAH100A2102) when it is compared to the individual components administered simultaneously. The interaction is limited to the pharmacokinetic parameters for ALI which misses the accepted 90% CI of 80-125% only for $C_{max}$ (see Figure 1). The value for AUC marginally resides within the accepted bioequivalence limit. However, neither the confidence limits for the AUC nor for $C_{max}$ of ALI encompassed equivalence. These results suggest that in the common use of the word equivalent, the formulations were not. For Tekturna HCT® (the combination product of ALI and HCTZ; NDA 22-107) and Tekamlo® (NDA 22-545) (combination of AML/ALI) the CI of the bioequivalent margins are bioequivalent to the individual components.

**Figure 1: Pharmacokinetic parameters comparing Amturnide® to the individual components administered together**

**Table 1(a):** Summary of pharmacokinetic measures and parameters for aliskiren

| | Geometric mean (% CV) | |
|---|---|---|
| **PK parameter** | **Reference (Free, N=102)** | **Test (Fixed, N=103)** |
| $C_{max}$ (ng/mL) | 296.7 (62.2) | 252.8 (46.7) |
| $t_{max}$ (h)† | 2.0 (0.5 – 8.0) | 1.0 (0.5 – 6.0) |
| $AUC_{0\text{-}last}$ (h*ng/mL) | 2154 (39.8) | 1855 (39.8) |
| $AUC_{0\text{-}\infty}$ (h*ng/mL) | 2302 (39.2) | 1994 (40.1) |
| $t_{1/2}$ (h)‡ | 63.9 ± 13.3 | 66.0 ± 14.7 |

**Table 1(b):** Summary of pharmacokinetic measures and parameters for amlodipine

| | Geometric mean (% CV) | |
|---|---|---|
| **PK parameter** | **Reference (Free, N=100)** | **Test (Fixed, N=102)** |
| $C_{max}$ (ng/mL) | 3.05 (21.1) | 3.11 (22.2) |
| $t_{max}$ (h)† | 8.0 (4.0 – 12.0) | 8.0 (6.0 – 12.0) |
| $AUC_{0\text{-}last}$ (h*ng/mL) | 191.0 (26.2) | 191.4 (26.6) |
| $AUC_{0\text{-}\infty}$ (h*ng/mL) | 212.1 (29.6)[1] | 210.1 (29.1)[1] |
| $t_{1/2}$ (h)‡ | 54.6 ± 13.0 | 53.6 ± 13.5 |

**Table 1(c):** Summary of pharmacokinetic measures and parameters for HCTZ

| | Geometric mean (% CV) | |
|---|---|---|
| **PK parameter** | **Reference (Free, N=102)** | **Test (Fixed, N=103)** |
| $C_{max}$ (ng/mL) | 138.7 (25.5) | 132.2 (24.5) |
| $t_{max}$ (h)† | 2.0 (1.0 – 4.0) | 3.0 (1.5 – 6.0) |
| $AUC_{0\text{-}last}$ (h*ng/mL) | 1065.0 (22.8) | 1024.0 (22.8) |
| $AUC_{0\text{-}\infty}$ (h*ng/mL) | 1101.0 (21.3) | 1056.0 (21.8) |
| $t_{1/2}$ (h)‡ | 9.6 ± 1.1 | 9.6 ± 1.1 |

† *Median (range);* ‡ *Mean ± SD;* [1] *N=93*

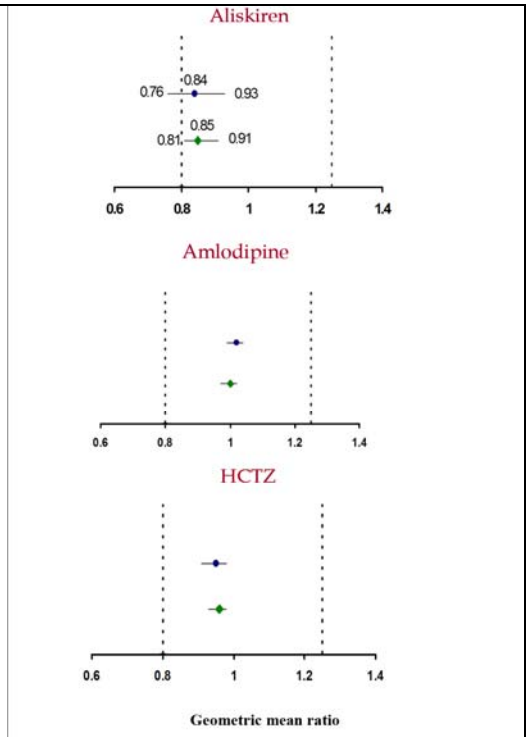



**Figure 1:** Results of the statistical analysis. X-axis represents the geometric mean ratios. The broken vertical lines represent the pre-determined BE limits. Data is represented as geometric mean ratio of the BE metrics ($C_{max}$, $AUC_{0\text{-}last}$, $AUC_{0\text{-}\infty}$) with 90% CI around the point estimate.

The effect of the maximal strength of the triple combination (particularly the 10 mg dose of AML) on the kinetics of ALI is not known.

During the pivotal clinical trial subjects were randomized to receive either the three dose combination or one of the three possible two-dose combinations. Pharmacokinetic measurements were collected after subjects were at steady state of the highest dose of the triple combination. There were a total of 70 subjects who had pharmacokinetic measurements (there were 17 to 23 in each of the four possible treatment groups).

The results are shown below.

**Table 2 Pharmacokinetic parameters from PK substudy of SAH 2302, mean ± SD**

| Amlodipine | | | |
|---|---|---|---|
| | In ALI/AML/HCTZ | In AML/HCTZ | In ALI/AML |
| N | 17 | 19 | 18 |
| $AUC_{0-24}$ | 441 ± 175 | 397 ± 164 | 341 ± 157 |
| $C_{max}$ | 17.5 ± 8.6 | 20.7 ± 7.9 | 18 ± 7.9 |
| | | | |
| Aliskiren | | | |
| | In ALI/AML/HCTZ | In ALI/HCTZ | In ALI/AML |
| N | 17 | 23 | 18 |
| $AUC_{0-24}$ | 1408 ± 1009 | 1362 ± 847 | 1530 ± 1116 |
| $C_{max}$ | 245 ± 235 | 214 ± 96 | 294 ± 311 |
| | | | |
| HCTZ | | | |
| | In ALI/AML/HCTZ | In ALI/HCTZ | In AML/HCTZ |
| N | 17 | 23 | 19 |
| $AUC_{0-24}$ | 1454± 654 | 1788 ±856 | 1647 ± 822 |
| $C_{max}$ | 170 ± 51 | 190 ± 64 | 219 ± 95 |

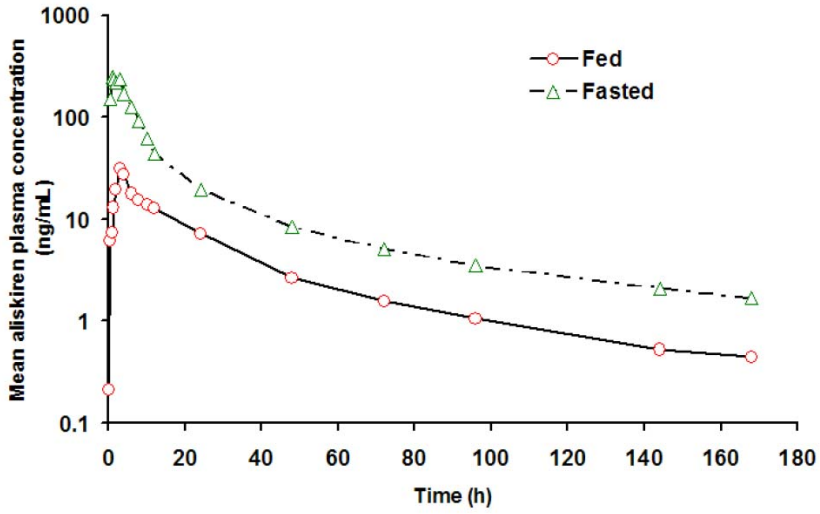
The above results show no difference in ALI concentrations when derived from the triple therapy for AUC or $C_{max}$. The study was small and the standard deviations are fairly large so that even large differences based on the concomitant therapies cannot be ruled out.

Whether there is interaction between the triple therapy and the individual components is more of an academic exercise than an approvability issue. The clinical trial clearly shows that the addition of the third component of the triple therapy increases the blood pressure lowering effect. The fact that the interaction indicates a less than equivalent exposure of ALI indicates that any additional blood pressure effect is not related to an increase in the exposure to one of the components.

The to-be marketed formulation is bioequivalent to the clinical trial formulation.

There is a large effect of a high-fat meal compared to fasting when the three-drug combination (to-be marketed formulation). The $C_{max}$ in the fasted state is approximately 8 fold higher fasted and the AUC is approximately 5-fold higher than in the fed-cohort. See figure 2.

**Figure 2 Pharmacokinetic profile for ALI in the triple therapy comparing fasted to fed.**



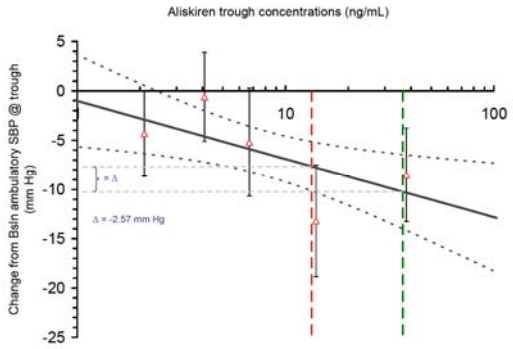

Mean aliskiren plasma concentration-time profile following single oral administration of 300/10/25 mg aliskiren/amlodipine/HCTZ fixed-dose combination tablet in fed vs fasted state

From Clinical Pharmacology review

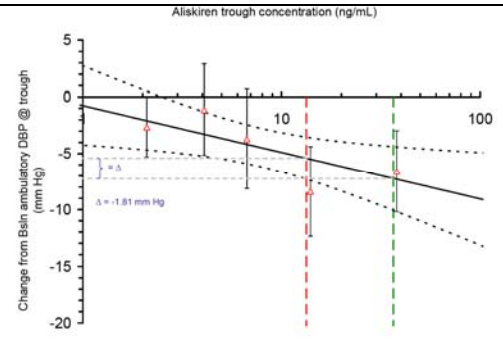
Should an instruction be included in labeling that suggests that the patient take the dual formulations fasted, if one of the components is ALI, before either increasing the dose or adding the third drug? Prior to initiating an additional antihypertensive therapy, optimizing ALI by taking the drug in the fasted state would seem appropriate. This algorithm would not be limited to the triple combination but would also apply to all combination products containing ALI.

The most important piece of missing information is what is the consequence of the large increase in the concentration of ALI on blood pressure effects? The clinical pharmacology group applied the following approach. They took the information contained in a study comparing the blood pressure effect of ALI (monotherapy) when compared to losartan (study #04 HTN DN of the Tekturna NDA 21-985). The doses of ALI were 37.5, 75, 150 and 300 mg. Ambulatory measurements of blood pressure were performed at baseline and end of therapy (week 4).Trough values were defined as the last 3 hours of the ABPM reading and these values for SBP and DBP were subtracted from the corresponding measurements at baseline. Concentrations of ALI were simultaneously measured at the inter-dosing interval. The log-dose relationship of acute ALI concentration versus trough effect is shown below (Figure 1A of the Clinical Pharmacology review). The green and red vertical lines correspond to the trough estimated for the 300 mg dose fed and 300 mg dose fasted. The concentrations of ALI were subdivided into quintiles independent of the dose administered. The point estimate for the difference in effect modeled to the concentration with and without food is -2.57 mmHg for SBP and -1.81 mmHg for the DBP. The effect of food is smaller than and cannot account for the additional effect of triple therapy on measured SBP. The effect on

DBP is more problematic and the food effect may account for a substantial portion of the observed BP effect.




Exposure-change from baseline ambulatory SBP relationship of aliskiren. X-axis represents aliskiren trough plasma concentrations and Y-axis represents corresponding mean change from baseline ambulatory SBP at trough. Red triangles represent the median aliskiren trough plasma concentration in each pentile21 plotted against the corresponding mean change from baseline ambulatory SBP at trough. Error bars represent 95% CI around the mean. The solid line represents the log-linear fit modeled through the entire dataset with 95% CI represented by dotted lines. Red and green vertical dashed lines represent the median steady state trough concentration in fed and fasted state following aliskiren 300 mg QD.




Exposure-change from baseline ambulatory DBP relationship of aliskiren. X-axis represents aliskiren trough plasma concentrations and Y-axis represents corresponding mean change from baseline ambulatory DBP at trough. Red triangles represent the median aliskiren trough plasma concentration in each pentile21 plotted against the corresponding mean change from baseline ambulatory DBP at trough. Error bars represent 95% CI around the mean. The solid line represents the log-linear fit modeled through the entire dataset with 95% CI represented by dotted lines. Red and green vertical dashed lines represent the median steady state trough concentration in fed and fasted state following aliskiren 300 mg QD.

From Clinical Pharmacology review

The underlying assumption for this sort of analysis is that the effect on blood pressure is intimately related to acute concentrations of ALI. Since there is a long washout of effect on BP after cessation of therapy (see study 2308 of the Tekturna® NDA), there is some reason to question such an assumption.

An alternative approach to defining the effect of large concentrations swings on blood pressure can be assessed form the results of the dose response studies for the monotherapy of ALI (Tekturna®). The blood pressure response based on dose is shown below. There were 5 studies with data available. The pooled study results show that in the tested dose-range over approximately a factor of 8 there is a 3-fold increase in both the effect on both diastolic and systolic blood pressures. This would suggest that the concentration is not at the flattened portion of the dose response curve where the effect of concentration changes would be minimal. Table 1 and 2 show the effects of dose on systolic and diastolic blood pressures, respectively. Table 3 is a simplistic averaging of the studies.

**Table 3: Dose response results for Aliskiren monotherapy from NDA 21-985**

**Table 14: Reviewer's Placebo-Subtracted Change from Baseline in Seated Trough Cuff SBP in the Five Pivotal Studies**

| Study | Median Group n | Placebo | Placebo-subtracted SBP change | | | | Comment |
|---|---|---|---|---|---|---|---|
| | | | 75 | 150 | 300 | 600 | |
| 1201 | 114 | -2.9 | -5.7* | -5.8* | -11.2* | | Japanese |
| 2201 | 130 | -5.3 | | -10.5* | -10.4* | -7.2 | Different formulation |
| 2203 | 177 | -10 | -2.1 | -2.1 | -5.1* | | 75, 150 encapsulated |
| 2204 | 185 | -7.5 | -1.9 | -4.7* | -8.2* | | 75, 150 encapsulated |
| 2308 | 169 | -3.8 | | -9.2* | -10.9* | -12.0* | |

*p<0.05 vs. placebo by ANCOVA with Dunnett's procedure for multiple comparisons

**Table 1: Reviewer's Placebo-Subtracted Changes from Baseline in Seated Trough Cuff DBP in the Five Pivotal Studies**

| Study | Median Group n | Placebo | Placebo-subtracted DBP change | | | | Comment |
|---|---|---|---|---|---|---|---|
| | | | 75 | 150 | 300 | 600 | |
| 1201 | 114 | -3.3 | -3.9* | -4.5* | -7.4* | | Japanese |
| 2201 | 130 | -6.3 | | -3.0* | -5.5* | -5.2* | Different formulation |
| 2203 | 177 | -8.6 | -1.7 | -1.7 | -3.7* | | 75, 150 encapsulated |
| 2204 | 185 | -6.9 | -1.8 | -2.0* | -3.4* | | 75, 150 encapsulated |
| 2308 | 169 | -4.9 | | -5.4* | -6.2* | -7.6* | |

*p<0.05 vs. placebo by ANCOVA with Dunnett's procedure for multiple comparisons

**Table 4: Pooled dose response effect Aliskiren monotherapy**

| Parameter↓ Dose→ | 75 mg/day | 150 mg/day | 300 mg/day | 600 mg/day |
|---|---|---|---|---|
| SBP | 3.2 | 6.5 | 9.2 | 9.6 |
| DBP | 2.4 | 3.2 | 5.2 | 6.4 |

The table below shows the dose relationship between doses of ALI monotherapy to pharmacokinetic parameters.

**Table 5 Pharmacokinetic parameters Aliskiren NDA mean ± SD**

| Parameter↓ Dose→ | 75 mg/day | 150 mg/day | 300 mg/day | 600 mg/day |
|---|---|---|---|---|
| $C_{max}$ ng/ml | 26 ± 31 | 72 ± 62 | 202 ± 119 | 420 ± 325 |
| $AUC_{0-\infty}$ ng/ml*hr | 356± 217 | 627 ± 401 | 1620± 895 | 3520 ± 2130 |

Over this range of doses, the exposure (AUC) to ALI appears to be approximately or slightly greater than linear. The results are taken from the clinical pharmacology review of Tekturna® (Aliskiren monotherapy) and are the results of a single-dose cross-over study.

Taken as a whole with a large number of caveats, the clinical efficacy data seem to suggest that for ALI, the range generated in the clinical trials still demonstrates that there is a dose-response or an exposure-response relationship to blood pressure effect. Given an 5-fold food effect on AUC, one could estimate that there is somewhere around a 3.1-6 mm Hg effect on SBP (compare the effect at either 75 to that of 300 mg; or compare the 150 to the 600 mg dose) and an effect of 2.8 to 3.2 for DBP.

It seems reasonable to conclude that the process of taking ALI or any of the combination products containing ALI with food has consequence to the blood pressure effect. The magnitude of this effect appears to be uncertain but is not likely to be trivial. The most important of the studies would be to define whether there are marked blood pressure effects of taking ALI or its combinations with or without food.

Clinical study:

The efficacy of the triple combination of ALI/AML/HCTZ is driven primarily by the results of study SAH 2302. The study was an 8-week double-blind, parallel group, controlled study, comparing effect of each of the two-therapy treatments with that of the triple therapy. Two of the three dual combinations are currently approved (ALI/HCTZ and ALI/AML); the other dual therapy combinations (AML/HCTZ) is not approved. The study planned to enroll approximately 246 subjects to each of the four treatment arms (ALI/HCTZ; ALI/AML; HCTZ/AML; and ALI/AML/HCTZ). The study enrolled subjects with moderate to severe hypertension with reproducible blood pressure measurements at 2 adjacent baseline visits as judged by the following criteria:

- Diagnosis of moderate to severe hypertension (SBP ≥ 160 mmHg and < 200 mmHg, and/or DBP ≥ 100 mmHg and < 120 mmHg) at Visits 4, 5 or 6 (qualifying BP visit);
- In addition, at the visit immediately prior to the above qualifying visit, patients were also to have SBP ≥ 145 mmHg and < 200 mmHg and DBP ≥ 95 mmHg and < 120 mmHg) at Visits 3, 4 or 5;
- Patients had to meet the above two sets of requirements at subsequent adjacent visits, i.e. either visits 3 and 4, visits 4 and 5, or visits 5 and 6.

OR a single extremely high measurement of BP defined as:

- SBP ≥ 180 mmHg and < 200 mmHg with DBP ≥ 95 mmHg and < 120 mmHg, or DBP ≥ 110 mmHg and < 120 mmHg with SBP ≥ 150 mmHg and < 200 mmHg after at least one week of treatment with placebo (visit 3 or later on).

Subjects were dosed for 4 weeks with half the randomized dose (150 ALI/5AML; 150 ALI/12.5 HCTZ; 5 AML/12.5 HCTZ or 150 ALI/5 AML/12.5 HCTZ) followed by the escalation to the full dose for the remaining 4 weeks.

The primary metric of the study was change in cuff measurements of trough SBP at the end of the 8 week period (4 weeks at full dose). For missing 8-week data the LOCF method was employed to impute the missing blood pressure measurement. An analysis of covariance model with treatment and region as the two factors and baseline as the covariate was the primary analytic method. Three pair-wise comparisons of each of the dual therapies compared to the triple therapy were made. A significant effect was if the two-sided test for the triple combination was greater with a p-value of < 0.05 for all three comparisons of the triple therapy to each of the dual therapies. In addition to cuff measurements, 143 subjects/treatment group were to have ABPM measurements performed at baseline and end of 8-week randomized-portion of the study.

There were 1191 subjects who were enrolled. Some demographic characteristics are shown below.

**Table 6 Selected demographic baseline characteristics study SAH 2302**

| Treatment group→ Parameter↓ | AML/ALI/HCTZ | ALI/AML | ALI/HCTZ | AML/HCTZ |
|---|---|---|---|---|
| N= | 310 | 287 | 298 | 296 |
| Age ± SD | 55.4 ± 10.5 | 54.4 ± 11 | 55.5 ± 10.8 | 55.1 ±10.9 |

| | | | | |
|---|---|---|---|---|
| ≥65 years (N)<br>≥ 75 years (N) | 59 (19%)<br>11 (4%) | 50 (17%)<br>10 (3%) | 56 (19%)<br>13 (4%) | 63 (21%)<br>8 (3%) |
| Gender (% female) | 40% | 40% | 41% | 37% |
| Ethnicity % non-Caucasian | 47 (15%) | 43 (15%) | 47 (16%) | 52 (18%) |
| SBP baseline mean sitting ± SD | 171.7 ± 13 | 171.5 ± 13 | 173.1 ± 14 | 173.2 ± 13 |
| DBP baseline mean sitting ± SD | 103.4 ± 8 | 104.9 ± 7 | 103.3 ± 7 | 103.6 ± 7 |

Derived from sponsor's table 11-2 and 11-3 of study report

The groups were well balanced. The proportion of elderly ≥ 65 were approximately 19%; there were few subjects ≥75 years. The percent of black patients in the database was approximately 10%.

Disposition:

The disposition of patients during the 8 week trial is shown below:

**Table 7 Disposition of subjects study SAH 2302**

| Treatment group→<br>Parameter↓ | AML/ALI/HCTZ | ALI/AML | ALI/HCTZ | AML/HCTZ |
|---|---|---|---|---|
| Randomized | 310 | 287 | 298 | 296 |
| Completed | 285 (92%) | 266 (93%) | 276 (93%) | 279 (94%) |
| Discontinued | 24 (8%) | 21 (7%) | 21 (7%) | 27 (6%) |
| Reason for discontinuation | | | | |
| Adverse events | 11 (4%) | 7 (2%) | 2 (1%) | 8 (3%) |
| Abnormal lab or test | 2 (1%) | 1 (< 1%) | 3 (1%) | 2 (1%) |
| Unsatisfactory effect | 2 (1%) | 2 (1%) | 3 (1%) | 1 (<1%) |
| Protocol deviation | 0 | 2 (1%) | 0 | 1 (<1%) |
| Withdrew consent | 8 (3%) | 5 (2%) | 7 (2%) | 3 (1%) |
| Lost to follow-up | 1 (<1%) | 4 (1%) | 6 (2%) | 2 (1%) |

Since this was a short-term study with only 4 weeks at the maximal dose, it is not surprising that there were few dropouts due to adverse events. There were nominally more dropouts in the triple therapy group than in the dual therapy groups.

Efficacy measurements:

The comparison of triple therapy to each of the dual therapies is shown below:

**Table 8: The blood pressure effect of triple therapy versus dual therapy based on ITT. Lower section of table contains similar analysis limited to those whose BP measurements were performed as per protocol.**

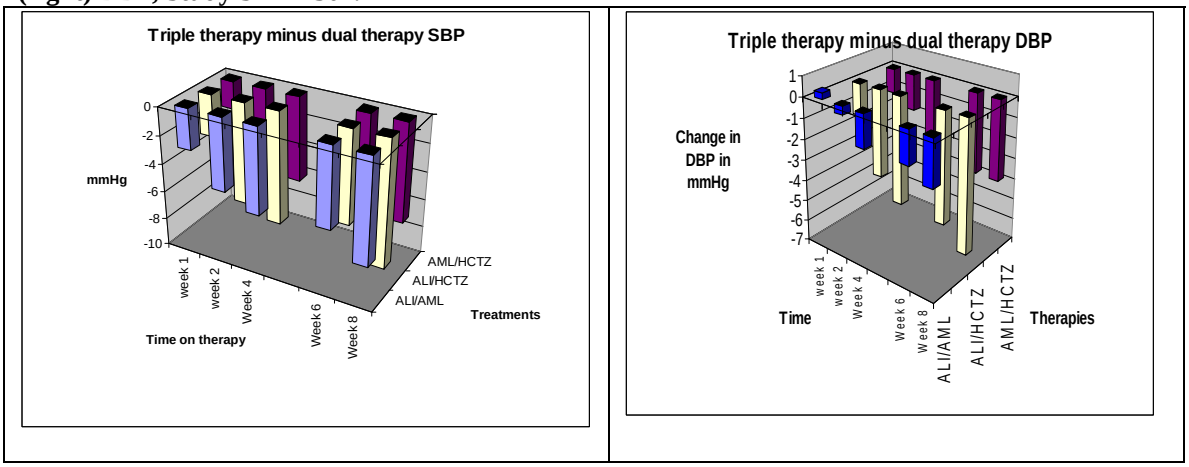
| Treatment group→<br>Parameter↓ | AML/ALI/HCTZ<br>versus ALI/AML | AML/ALI/HCTZ<br>versus ALI/HCTZ | AML/ALI/HCTZ<br>sus AML/HCTZ |
|---|---|---|---|
| SBP | -6.55* | -9.93* | -7.15* |
| DBP | -2.60* | -6.31* | -3.60* |
| * p<0.001 | | | |
| Analysis excluding subjects not appropriately screened+ | | | |
| SBP | -8.3 | -12.6 | -10.1 |
| DBP | -1.4 | -8.3 | -4.2 |

+ The sponsor analyzed the data for those whose BP measurements were out of protocol specifications for the whole database and not just the study sites visited by the EMEA.

The effect of triple therapy compared to each of the dual therapies was clearly superior in its effect on SBP. The effect on DBP for the whole population was less convincing. Nevertheless, each of the primary comparisons at endpoint (SBP) was significant. The time course is shown below. At week 4 the comparison is between half-

doses of triple therapy to half doses of each of the dual therapies. At week 6-8 the comparison is full doses. The effect size is not that different from the effect size at week 4.

**Figure 3 Time course of triple therapy effects compared to dual therapy effects (left) effect on SBP, (right) DBP, Study SAH 2302.**

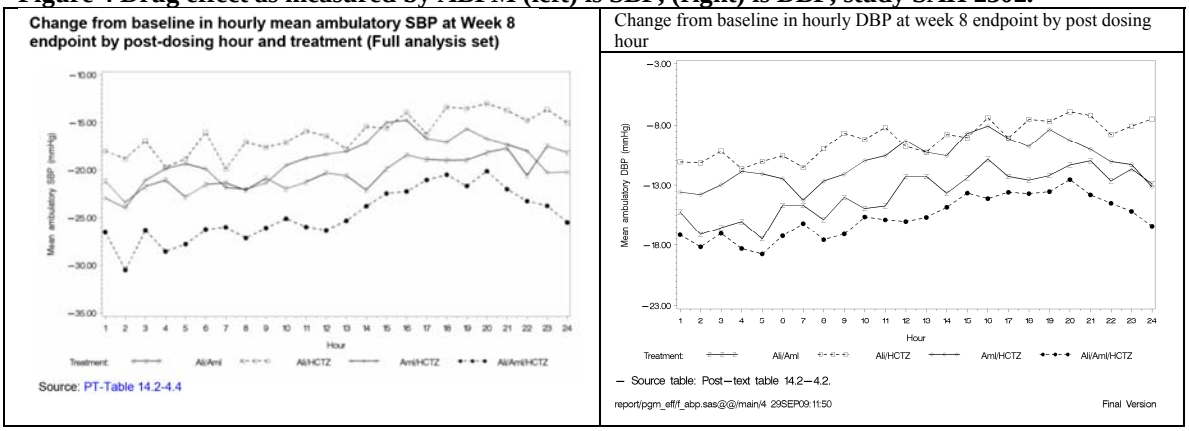



The full effect on blood pressure of the triple therapy appears to take greater than 2 weeks.

ABPM:

The change from baseline in blood pressure for SBP and DBP for ABPM measurements is shown below. All three dual therapy groups demonstrate a substantial change from baseline. The triple therapy drug effect was greater than each of the dual therapy groups throughout the inter-dosing interval. For diastolic blood pressure, the effect of ALI/AML is nearly equivalent to the triple therapy.

**Figure 4 Drug effect as measured by ABPM (left) is SBP, (right) is DBP, study SAH 2302.**






Subgroups:

Most of the subgroups effects are under-powered to adequately assess whether the sub-population differs from the effect as a whole. With respect to gender race and age, the results are shown below:

**Table 9: Triple therapy effect compared to dual therapy effect for subgroups, mean (95% CI), study SAH2302**

| | Triple therapy versus | | |
|---|---|---|---|
| | ALI/AML | ALI/HCTZ | AML/HCTZ |
| Gender | | | |
| Male | -5.7 (-8.6, -2.8) | -8.3 (-11.2, -5.4) | -7.1 (-10.0, -4.2) |
| Female | -7.7 (-11.6, -3.9) | -12.4 (-16.2, -8.7) | -6.5 (-10.4, -2.8) |
| Race | | | |
| Caucasian | -6.7 (-9.3, -4.1) | -9.4 (-12.0, -6.8) | -6.3 (-9.0, -3.7) |
| Black | -5.6 (-13.6, ±2.4) | -10.4 (-17.9, -2.8) | -9.8 (-17.2, -2.5) |
| Asian | -2.9 (-17.9, ± 12.1) | -19.1 (-33.8, -4.3) | -19.1 (-24.1, ± 6.1) |
| Age | | | |
| < 65 years | -6.3 (-8.87, -3.6) | -9.6 (-12.2, -7.0) | -6.3 (-8.9, -3.7) |
| 65 to > 75 years | -5.7 (-12.5, ± 1.05) | -10.6 (-17.4, -3.7) | -8.5 (-14.8, -2.2) |
| ≥ 75 years | -14.8 (-29.6, -0.1) | -15.5 (29.4, -1.6) | -20.6 (-37.0, -4.2) |

Safety:

Amturnide® is the combination product of three well known and approved therapies. The safety profile is likely to encompass the known adverse events from each of the individual components.

Empirical safety information is derived largely from the short term comparison of triple therapy to each of the three dual-treatment therapies. The duration of time at the highest dose was short (4 weeks) and not surprisingly, the study is not very discriminatory in the description of adverse events. In addition, safety data is derived form study SAH1002301. This study was an open-label, multinational, multicenter, forced titration study to achieve dosing with ALI 300/AML10/HCTZ 25.

The study enrolled 564 subjects with essential hypertension with seated DBP > 100 and < 120 mmHg and/or seated SBP > 160 and < 200 m Hg. The study had an approximately 1 week of half-dose therapy followed by the targeted dose for between 28-54 weeks.

The demographics of this study were similar to the population studied in the controlled trial.

**Table 10: Demographics for open-label study SAH1002301**

| Parameter (n=564) | |
|---|---|
| Age mean ± SD | 55.9 ± 11.3 |
| < 65 years old, n (%) | 429 (76%) |
| ≥ 65 years, n (%) | 135 (23.9%) |
| ≥ 75 years, n (%) | 25 (4.8%) |
| Gender male, n (%) | 326 (58%) |
| Race | |
| Caucasian, n (%) | 507 (90%) |
| Black, n (%) | 42 (7%) |
| Asian, n (%) | 10 (2%) |
| Other, n (%) | 5 (1%) |

The disposition of the subjects in this study is shown below:

**Table 11 Disposition of subjects in study SAH1002301**

| | |
|---|---|
| Entered | 564 (100%) |
| Completed | 493 (87%) |
| Discontinued | 71 (13%) |
| Adverse events | 39 (7%) |
| Abnormal test procedure | 1 (< 1%) |
| Unsatisfactory therapeutic effect | 3 (1%) |
| Protocol deviation | 3 (1%) |
| Consent withdrawn | 17 (3%) |
| Lost to follow-up | 8 (1%) |

The median duration of therapy was approximately 236 $\pm$ 101 days at the high dose. The duration of treatment at other doses are approximately 7 days. Approximately 7% discontinued for adverse events in this approximately 8 month period.

Deaths, dropouts and discontinuations:

There were no deaths in this study. There were 15 subjects in the whole study who were discontinued due to serious adverse events:

**Table 12: Description of serious adverse events study SAH1002301**

| | Subject ID | Demographics | Description |
|---|---|---|---|
| 1 | -307-00006 | 38/W/M | On day 18 was hospitalized for left arm pain (? r/o MI). Tests were described as negative |
| 2 | -0201-00007 | 48/W/M | On day 96 had an incarcerated inguinal hernia, requiring surgery. On day 104 he developed thrombophlebitis, treated with anti-coagulation. |
| 3 | -0205-00009 | 56/ W/F | Hospitalized for paresthesia diagnosed as cervical spine stenosis. An ultrasound of the abdomen noted hepatic steatosis. |
| 4 | -0256-00002 | 79/W/M | On day 88 developed bronchitis and was hospitalized. Subject developed on day 209 edema of the legs. He had second episode of infectious bronchitis on day 336. |
| 5 | -0264-00007 | 75/W/F | Patient developed hip arthrosis requiring surgery. |
| 6 | -0401-00001 | 62/W/F | Patient had lumbar hernia disk repair. |
| 7 | -0456-00003 | 52/W/F | On day 26 this patient had heart palpitations resulting in hospitalization (ECG report not included). |
| 8 | -0501-00007 | 68/W/M | Had symptoms of TIA on day 168, had right carotid endarterectomy. |
| 9 | -0501-00009 | 52/W/F | On day 361 had episode of ECG defined atrial fibrillation. |
| 10 | -0502-00001 | 41/B/F | On day 43 had hypokalemia (K+ 3.4 mmol/L. On day 159 subject hospitalized for chest pain and CT-diagnosed sinusitis. Also diagnosed was renal insufficiency. The HCTZ component of therapy was discontinued. On day 167 the patient was hospitalized for pre-syncope. |
| 11 | -0506-00003 | 52/B/F | On day 108 this subject was hospitalized for planned bilateral hip replacement. |
| 12 | -0508-00002 | 76/W/F | Patient developed shortness of breath on day 115. Chest x-ray showed interstitial pattern. WBC was not particularly high. She was treated with antibiotics and recovered. She discontinued study. |
| 13 | -0512-00012 | 43/W/F | On day 318 discontinued due to Xanax and Vicodin dependence. |
| 14 | -0517-00006 | 48/W/M | Patient with history of diabetes developed ischemic left toe (day 354) apparently recovered. |
| 15 | -0700-00013 | 54/W/M | On day 70 patient developed right-sided hemiparesis and resulted in hospitalization. MRI showed right basal ganglia infarction. |

There does not appear to be a convincing pattern of serious adverse events. There were two cerebrovascular events (one a TIA). There were two palpitation/atrial fibrillation events. Of note there was one subject who developed hypokalemia and subsequently developed renal insufficiency.

The most common non-serious adverse event leading to discontinuation was peripheral edema (13 events); hypotension and tachycardia were the cause of

discontinuation in 4 and 3 subjects, respectively. These are common adverse events for AML (edema) and antihypertensive therapies, in general (headache, dizziness, and vertigo).

The most frequent adverse events from study SAH2301 are shown below:

**Table 13 Non-serious adverse event study SAH1002301**

| Event | Any dose of AML/ALI/HCTZ |
|---|---|
| Edema peripheral | 52 (9%) |
| Headache | 22 (4%) |
| Nasopharyngitis | 21 (4%) |
| Bronchitis | 20 (4%) |
| Diarrhea | 12 (2%) |
| Dizziness | 12 (2%) |
| Vertigo | 13 (2%) |

Laboratory values as change from baseline to last visit are shown below.

**Table 14: Laboratory values baseline, end of therapy and change from baseline study SAH1002301**

| | Units | Baseline | End of treatment | Change |
|---|---|---|---|---|
| Hematology | | | | |
| Hemoglobin | g/dL | 14.1 ± 1.3 | 14.2 ± 1.3 | 0.06 ± 0.8 |
| Hematocrit | (%) | 43 ± 4.2 | 44 ± 4.4 | 0.8 ± 4 |
| Platelet | x $10^9$/L | 253 ± 62 | 370 ± 65 | 17 ± 42 |
| WBC | x $10^9$/L | 6.6 ± 1.7 | 6.7 ± 1.8 | 0.08 ± 1.3 |
| Chemistry | | | | |
| Sodium | Mmol/L | 140 ± 2.2 | 140 ± 2.2 | -0.2 ± 2.3 |
| Potassium | Mmol/L | 4.3 ± 0.4 | 4.2 ± 0.5 | -0.1 ± 0.5 |
| Blood urea nitrogen | mmol/L | 5.6 ± 1.6 | 6.0 ± 1.8 | 0.49 ± 1.5 |
| Creatinine | µmol/L | 80.2 ± 17 | 81.7 ± 18 | 1.5 ± 11 |
| Glucose | mmol/L | 6.2 ± 1.8 | 6.5 ± 2.1 | 0.35 ± 1.4 |
| AST | U/L | 24.8 ± 12 | 25.2 ± 12 | 0.4 ± 9 |
| Alkaline phosphatase | U/L | 73 ± 22 | 72 ± 20 | -0.8 ± 13 |
| Calcium | mmol/L | 2.4 ± 0.11 | 2.3 ± 0.12 | -0.01 ± 0.1 |
| Phosphate | mmol/L | 1.08 ± 0.18 | 1.09 ± 0.8 | 0.00 ± 0.17 |
| Uric acid | mcgM/L | 341 ± 83 | 373 ± 94 | 32 ± 68 |

The key changes of note were an increase in creatinine and BUN. Glucose and uric acid increases may be attributable to the diuretic component.

In summary, there does not appear to be a signal that the safety events with Amturnide® qualitatively differ from the safety signals of its individual components. It is difficult to determine whether there are quantitative differences in adverse events when the triple therapy is used relative to the individual monotherapies..

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/s/

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ABRAHAM M KARKOWSKY
12/10/2010