HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

6 February 2008

RASILEZ 150 mg, film-coated tablets
Boxes of 28, CIP Code: 382 098-5
Boxes of 30, CIP Code: 381 536-9

RASILEZ 300 mg, film-coated tablets
Boxes of 28, CIP Code: 382 099-1
Boxes of 30, CIP Code: 381 537-5

Applicant: NOVARTIS PHARMA SAS

aliskiren
ATC code: C09XA02

List I

Date of marketing authorization: 22 August 2007 (centralized MA)

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for hospital use.

Health Technology Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Aliskiren

1.2. Originality
Aliskiren is the first direct renin inhibitor.

1.3. Indication
"Treatment of essential hypertension (HT)."

1.4. Dosage
The recommended dose of Rasilez is 150 mg once daily. In patients whose blood pressure is not adequately controlled, the dose may be increased to 300 mg once daily.
The antihypertensive effect is substantially present within two weeks (85-90%) after initiating therapy with 150 mg once daily.
Rasilez may be used alone or in combination with other antihypertensive agents.
Rasilez should be taken with a light meal once a day, preferably at the same time each day.

Renal impairment: No adjustment of the initial dose is required for patients with mild to severe renal impairment.

Hepatic impairment: No adjustment of the initial dose is required for patients with mild to severe hepatic impairment.

Elderly patients (over 65 years): No adjustment of the initial dose is required for elderly patients.

Children and adolescents (below 18 years): Rasilez is not recommended for use in children and adolescents below age 18 due to a lack of data on safety and efficacy.

2. COMPARABLE MEDICINAL PRODUCTS

2.1. ATC Classification 2007
C : Cardiovascular system
09 : Agents acting on the renin-angiotensin system
X : Other agents acting on the renin-angiotensin system
A : Renin-inhibitors
02 : aliskiren

2.2. Medicines in the same therapeutic category
There are no medicinal products in the same therapeutic category.

2.3. Medicines with a similar therapeutic aim
Other medicinal products indicated in the treatment of essential hypertension:
- classes of medicinal products which have been demonstrated to reduce cardiovascular morbidity and mortality: beta-blockers, diuretics, calcium channel blockers, ACE inhibitors and sartans.
- classes of medicinal products which have not demonstrated any benefit in terms of mortality: alpha-blockers and central antihypertensive products.

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The evaluation of the efficacy and safety of RASILEZ is based on:

- two placebo-controlled trials
- eight controlled trials vs. active comparators (3 conducted with RASILEZ monotherapy and 5 in combination with other antihypertensive products).

In these trials, with the exception of trial 2324, the primary endpoint was the mean reduction in diastolic blood pressure (DBP) compared with the baseline value; the reduction in systolic blood pressure was evaluated as a secondary endpoint.

The file also includes:

- three phase II placebo-controlled trials (trials 1201[1], 2201[2], 2203[3]),
- two trials whose primary objective was to evaluate safety (non-comparative trial 2302 and trial 2303),
- a pooled analysis of the placebo-controlled trials whose objective was to evaluate the efficacy and safety of RASILEZ in certain sub-groups of patients defined *a posteriori* (gender, race, age).

All these trials were conducted in patients suffering from mild to moderate hypertension, with the exception of trial 2303 (patients with severe hypertension), the primary objective of which was to evaluate safety.

Only the placebo-controlled comparative trials or comparative trials vs. active treatments will be discussed in this opinion. Dose-finding studies will not be discussed.
Only the results relating to the primary endpoints will be presented.

3.1.1. Placebo-controlled trials

A phase III trial (2308[4]) was conducted with RASILEZ monotherapy in patients with mild to moderate hypertension (mean DBP at baseline between 95 and 110 mm Hg).

Another phase III trial (2309[5]) was conducted with RASILEZ combined with hydrochlorothiazide (HCTZ) in patients with mild to moderate hypertension (mean DBP at baseline between 90 and 110 mm Hg).
The methodological characteristics of these trials and their main results are presented in the annexed *table 1*.

In these trials, a significant reduction in DBP was observed with RASILEZ monotherapy or RASILEZ combined with HCTZ compared with the placebo.

3.1.2. Trials vs. active comparators

Eight trials vs. active comparators were conducted with RASILEZ in patients suffering from mild to moderate hypertension.

1 Kushiro et al. "Aliskiren, a novel oral renin inhibitor, provides dose-dependent efficacy and placebo-like tolerability in Japanese patients with hypertension", Hypertens. Res. 2006;29: 997-1005.
2 Gradman et al. "Aliskiren, a novel orally effective renin inhibitor provides dose-dependent efficacy and placebo-like tolerability in hypertensive patients" Circulation. 2005;111:1012-8.
3 Pool et al. "Aliskiren, an orally effective renin inhibitor provides antihypertensive efficacy alone and in combination with valsartan" AJH. 2007;20:11-20.
4 Oh et al. "Aliskiren, an oral renin inhibitor provides dose-dependent efficacy sustained 24-hour blood pressure control in patients with hypertension" J Am Coll Cardiol 2007;49:1057-63.
5 Jordan et al. "Direct renin inhibition with aliskiren in obese patients with arterial hypertension" Hypertension April 23, 2007;49:1-19.

Two of these trials were conducted with RASILEZ monotherapy: 2306[6] and 2323 (unpublished). The mean DBP at baseline had to be between 95 and 110 mm Hg.
The methodological characteristics of these two trials and their main results are presented in the annexed table 2.
In these trials, non-inferiority in terms of reduction in DBP was demonstrated between RASILEZ and:

- Ramipril: mean difference: -1.21 (± 0.54), 95% CI [-2.27;-0.15],
- Hydrochlorothiazide: mean difference: -1.22 (+ 0.43), 95% CI [-2.07;-0.36].

In a second analysis, a difference was observed between RASILEZ and:

- Ramipril: -1.21 (+ 0.54), 95% CI [-2.27;-0.15], p = 0.0250
- Hydrochlorothiazide: -1.22 mm Hg (+ 0.43), 95% CI [-2.07;-0.36], p = 0.0053.

In the absence of currently available comparative morbidity and mortality data, the clinical relevance of this superiority regarding the blood pressure figures remains to be confirmed.

Trial 2324 was conducted with RASILEZ monotherapy in patients over 65 years of age. The mean SBP at baseline had to be between 145 and 180 mm Hg (see *table 3* annexed). In this trial, no significant difference was observed between the arms tested (RASILEZ 75 mg/day, 150 mg/day and 300 mg/day).

The other five trials were conducted with RASILEZ in combination with other antihypertensive agents vs. another antihypertensive agent in combination with a placebo: 2204[7], 2305[8], 2304 (unpublished) and 2307[9], 2327[10]. The mean DBP at baseline had to be between 95 and 110 mm Hg except for trial 2305, in which the lower limit was set at 90 mm Hg.
The methodological characteristics of these five trials and their main results are set out in the annexed *table 4*.

These trials demonstrated the additional antihypertensive effect of RASILEZ combined with HCTZ, amlodipine, atenolol and valsartan.

With the exception of trial 2305, the increase in doses of RASILEZ and the use of bitherapy in these trials were independent of the patient's blood pressure status (forced titration).

3.2. Adverse effects

During these trials, 7896 patients were treated with RASILEZ.

The adverse events were generally mild and transient; discontinuance of the treatment was necessary in 2.3% of patients in the placebo-controlled trials and 2.4% of patients in the trials vs. active comparators.

The most frequent adverse event was diarrhoea, observed in 2.4% of the patients treated with RASILEZ and 1.2% of the patients who received the placebo.

In patients suffering from essential hypertension who were treated with RASILEZ monotherapy, increases in the blood potassium level were minor and infrequent (0.9 % vs. 0.6 % with the placebo).

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6 Andersen K et al. “Comparative efficacy and safety of aliskiren, an oral direct renin inhibitor, and ramipril in hypertension: a 6-month, randomized, double-blind trial” Journal of hypertension 2008,26:589-99.
7 Villamil et al. “Renin inhibition with aliskiren provides additive antihypertensive efficacy when used in combination with hydrochlorothiazide” Journal of hypertension 2007;25:217-26.
8 Drummond et al. “Antihypertensive efficacy of the oral direct renin inhibitor aliskiren as add-on therapy in patients not responding to amlodipine monotherapy” J. Clin. Hypertens. 2007;9:742-50.
9 Uresin Y et al. “Efficacy and safety of the direct renin inhibitor aliskiren and ramipril alone or in combination in patients with diabetes and hypertension” Journal of Renin Angiotensin Aldosterone System December 2007, volume 8:190-200.
10 Oparil et al. “Efficacy and safety of combined use of aliskiren and valsartan in patients with hypertension: a randomised, double-blind trial” Lancet July 31, 2007;370:221-9.

However, in a trial in which RASILEZ was used in combination with an ACE inhibitor, increases in the blood potassium level were more frequent (5.5%).

No serious adverse effects considered to be associated with the treatment were observed in these trials.
No safety data for pregnant women are available. However, in view of the risk of severe foetal malformations and neonatal death associated with other substances which act directly on the renin-angiotensin system, RASILEZ should not be taken by pregnant women or women intending to become pregnant (see SPC).

There are no available safety data in patients with severe renal impairment (serum creatinine ≥ 150 µmol/l or 1.70 mg/dl in women and ≥ 177 µmol/l or 2.00 mg/dl in men, and/or estimated glomerular filtration rate (GFR) < 30 ml/min). Patients suffering from severe kidney failure treated with RASILEZ should be carefully monitored (see SPC).

3.3. Conclusion

In patients with mild to moderate hypertension, the administration of RASILEZ 150 mg/day and 300 mg/day led to dose-dependant reductions in DBP (primary endpoint, see annexed tables). The results observed for SBP (secondary endpoint) were consistent with those obtained for DBP.

The trials conducted with RASILEZ monotherapy (2306 and 2323) demonstrated firstly the non-inferiority, and subsequently the superiority, in terms of blood pressure levels, of RASILEZ compared with ramipril and hydrochlorothiazide. These two analyses were specified in the trial plan. However, in the absence of currently available comparative morbidity and mortality data, the clinical relevance of this superiority regarding blood pressure values remains to be confirmed.

The trials conducted with RASILEZ in combination with other antihypertensive agents demonstrated an additional antihypertensive effect of RASILEZ compared with hydrochlorothiazide (trials 2204 and 2309) and ramipril (trial 2307).
Trials 2304, 2305 and 2327 also showed a significant reduction of DBP in patients treated with:

- RASILEZ 300 mg/atenolol 100 mg vs. RASILEZ 300 mg ($p<0.001$). Conversely, no difference vs. atenolol 100 mg alone was observed,
- RASILEZ 150 mg/amlodipine 5 mg vs. amlodipine 5 mg ($p<0.0001$),
- RASILEZ 300 mg/valsartan 320 mg vs. RASILEZ 300 mg monotherapy and valsartan 320 mg monotherapy ($p<0.001$).

With the exception of trial 2305, increased doses of RASILEZ and the use of bitherapy in these trials were independent of the patient's blood pressure status (forced titration).

In the trials as a whole, the mean age of the patients was 55 years; only one study was conducted on patients aged over 65 years.
All these trials were conducted on patients suffering from mild to moderate hypertension, with the exception of trial 2303 (patients with severe hypertension), the primary objective of which was to evaluate safety.
The efficacy of RASILEZ has been demonstrated for a surrogate endpoint, ie. reduction of diastolic blood pressure, but it has not yet been demonstrated for a clinical endpoint of morbidity and mortality.

The Committee has not received any trial in which the primary objective was to compare RASILEZ with other classes of antihypertensive agents whose benefit in terms of cardiovascular morbidity and mortality has been demonstrated (diuretics, sartans, beta-blockers; calcium channel blockers).

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

In view of its complications, hypertension can be life-threatening.

This proprietary drug is intended to provide preventive treatment.

The efficacy/adverse effects ratio for this medicinal product, evaluated on the basis of reduction in blood pressure levels, is high.

There are alternative drugs available.
The therapeutic needs are covered by other antihypertensive agents (thiazide diuretics, beta-blockers, calcium channel blockers, ACE inhibitors and angiotensin II receptor antagonists). In the absence of proof of a reduction in morbidity and mortality, RASILEZ must currently be classed as a second-line treatment.

> Public health benefit :
> The public health burden represented by essential hypertension and the cardiovascular disorders for which it constitutes a risk factor is high.
> Reducing the morbidity and mortality attributable to hypertension constitutes a public health need (a priority identified by the GTNDO and the Public Health Act).
> The available data based on an intermediate endpoint (DBP and SBP) do not allow quantification of the impact of RASILEZ in terms of reducing cardiovascular morbidity and mortality compared with antihypertensive agents which have already demonstrated such a benefit. According to the state of the art, therefore, RASILEZ cannot be deemed to provide a response to the need identified.
> Consequently, no public health benefit is expected for RASILEZ.

The actual benefit of this proprietary product is substantial.

4.2. Improvement in actual benefit

RASILEZ does not provide any improvement in actual benefit (IAB V) in the pharmacological treatment of essential hypertension. It represents a useful additional treatment.

4.3. Therapeutic use[11,12]

Diet and lifestyle measures are recommended for all patients suffering from hypertension, whatever their blood pressure levels, with or without associated pharmacological treatment.

Reducing cardiovascular risk is mainly dependent on reducing the blood pressure, whatever the class of antihypertensive used.

In essential hypertension without complications, some thiazide diuretics, some beta-blockers, some calcium channel blockers, some ACE inhibitors and some angiotensin II receptor antagonists have demonstrated a benefit in terms of cardiovascular morbidity and mortality in clinical trials.
These medicinal products can be offered as first-line treatment for essential hypertension without complications.

11 “Prise en charge des patients adultes atteints d’HTA” HAS Recommendations, July 2005.
12 Groupe de travail pour la prise en charge de l’hypertension de la Société Européenne d’Hypertension (ESH) et de la Société européenne de Cardiologie (ESC), Journal of Hypertension 2007;25 :1013-85.

As no benefit in terms of reducing morbidity and mortality has been demonstrated, the Committee considers that RASILEZ is a second-line treatment.

RASILEZ should not be taken by pregnant women and or women intending to become pregnant.

In the absence of safety data, patients suffering from severe renal impairment who are treated with RASILEZ must be closely monitored.

4.4. Target population

According to CNAMTS, the prevalence of treated hypertension was around 10.5 million patients in 2006 (source: EPAS, CNAMTS, October 2007).

30-50% of these treated patients are not "controlled" by their antihypertensive treatment (HAS Recommendations 2005, CNAMTS data 2007, and expert's opinion).

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion of the box of 30 tablets on the list of medicines reimbursed by National Insurance and approved for hospital use and various public services, for the indication and at the dosage specified in the marketing authorization, as a second-line treatment pending the availability of additional data.

The Committee does not recommend the inclusion of the box of 28 tablets.

4.5.1. Packaging:
Box of 30 appropriate for the prescription conditions
Box of 28 not appropriate for the prescription conditions

4.5.2. Reimbursement rate: 65%

List of abbreviations:
Ali: aliskiren (RASILEZ)
Amlo: amlodipine
Ate: atenolol
HCTZ: hydrochlorothiazide
Irb: irbesartan
Lis: lisinopril
Pbo: placebo
Ram: ramipril
Val: valsartan

Table 1 "Summary of phase III Rasilez monotherapy placebo-controlled trials"

Trial	Method	Patients	Treatment	Results	Conclusion
Monotherapy trial					
2308	Randomized, double-blind placebo-controlled trial (8 weeks) *Primary endpoint*: reduction in DBP vs. placebo	N=672 Mean age: 53 years mild to moderate hypertension	ali 150 mg/day, n=172 ali 300 mg/day*, n=169 ali 600 mg/day**, n=166 placebo, n=165	ali 150 mg/day vs placebo: -5.4 (±0.63) mmHg ali 300 mg/day vs placebo: -6.2 (±0.64) mmHg	Significant reduction in DBP with aliskiren (RASILEZ) vs. placebo p<0.0001
Trial in combination					
2309	Randomized, double-blind, placebo-controlled phase III trial (8 weeks) *Primary endpoint*: reduction in DBP HCTZ 25/ali 300 mg vs. HCTZ 25/placebo	N=487 Mean age: 65 years mild to moderate hypertension (90 < BP < 110 mmHg) *Obese patients*: Mean BMI 34± 4 kg/m²,	HCTZ / ali, n=122 HCTZ / amlo, n=126 HCTZ / irb, 119 HCTZ / Pbo, n=120	HCTZ 25 / Pbo: -7.89 mmHg (± 0.73) HCTZ 25/ali 300 : -11.91 mmHg (± 0.74) Mean difference -4.02 (SD: 1.02) 95% CI [-6.02;-2.01] p<0.0001	After 8 weeks' treatment: Significant reduction in DBP with HCTZ 25 /aliskiren (RASILEZ) 300 mg vs. HCTZ 25 mg/placebo, p<0.0001

* the dose of 300 mg/day must be reserved for patients not controlled by the dose of 150 mg/day

** off-label dose; the results are not presented

***Table 2* "Summary of trials with Rasilez monotherapy vs. active comparators"**

Trial	Method	Patients	Treatment	Results	Conclusion
2306	Randomized, double-blind, controlled trial vs. **ramipril** (26 weeks) *Primary endpoint*: reduction in mean DBP vs. ramipril (study of non-inferiority with a pre-defined non-inferiority margin of 2 mmHg, followed by study of superiority if non-inferiority is established)	N= 832 (ITT) Mean age: 53 years mild to moderate hypertension	Ali group, n=414 Ram group, n=418 The patients received aliskiren 150 mg or ramipril 5 mg for 6 weeks. If the BP was not controlled, the doses were increased to 300 and 10 mg for 6 weeks; 12.5 mg and 25 mg of HCTZ was added 6 and 12 weeks later if not controlled.	*Primary endpoint:* *Reduction in DBP after 26 weeks:* - ali: -13.17 mmHg - Ram: -11.96 mmHg Mean difference: -1.21 (± 0.54), 95% CI [-2.27;-0.15], p<0.0001 (not inferior) p = 0.0250 (superior)	The non-inferiority of aliskiren (RASILEZ) vs. ramipril was demonstrated at the first stage. The superiority of aliskiren (RASILEZ) to ramipril was demonstrated at the second stage.
2323	Randomized, double-blind, controlled trial vs. **HCTZ** (26 weeks) *Primary endpoint*: reduction in mean DBP vs. HCTZ (study of non-inferiority with a pre-defined non-inferiority margin of 2 mmHg, followed by study of superiority if non-inferiority is established)	N= 1,107 (ITT) Mean age: 56 years mild to moderate hypertension	Ali group, n=560 HCTZ group, n=547 The patients received aliskiren 150 mg or HCTZ 12.5 mg or placebo for 3 weeks. The doses were increased to 300 and 25 mg for 6 weeks; 5 mg and 10 mg of amlodipine was added 12 and 18 weeks later in the event of persistent non-control of the BP	*Primary endpoint:* *Reduction in DBP after 26 weeks:* - Ali group: -14.19 mmHg - HCTZ group: -12.97 mmHg Mean difference: -1.22 (± 0.43), 95% CI [-2.07;-0.36], p<0.0001 (not inferior) p = 0.0053 (superior)	The non-inferiority of aliskiren (RASILEZ) to HCTZ was demonstrated at the first stage. The superiority of aliskiren (RASILEZ) to HCTZ was demonstrated at the second stage.

Table 3* "*Summary of trial in elderly patients: Rasilez monotherapy at variable doses vs. lisinopril"

Trial	Method	Patients	Treatment	Results	Conclusion
2324	Randomized, double-blind trial (8 weeks) *Primary endpoint*: mean reduction in SBP in 24 hours with ABPM according to the dose of Ali used	N= 354 (ITT) Mean age: 73 years BP between 145 and 180 mmHg	ali 75 mg/day, n=91 ali 150 mg/day, n=84 ali 300 mg/day, n=94 lisinopril, n=85 (control arm)	*Primary endpoint:* Mean reduction in SBP over 24 hours with ABPM - ali 75: -8.35 mmHg (± 0.83) - ali 150: -7.06 mmHg (± 0.84) - ali 300: -8.67 mmHg (±0.80) - lis 10: -10.19 mmHg (± 0.86)	After 8 weeks' treatment: In elderly patients, no significant difference between aliskiren (RASILEZ) 150 mg/day and aliskiren (RASILEZ) 300 mg/day

Table 4 (page 1/2) "Summary of trials of Rasilez combined with another antiHTA vs. antiHTA only"

Trial	Method	Patients	Treatment	Results	Conclusion
Trials vs. separate administration					
2204	Phase II randomized, double-blind, multifactorial, placebo-controlled and **HCTZ**-controlled trial (8 weeks) *Primary endpoint*: reduction in DBP Ali vs. Pbo and ali+HCTZ vs. HCTZ and vs. ali	N= 2,752 (ITT) Mean age: 55 years mild to moderate hypertension	ali 75* mg, n=183 ali 150 mg, n=183 ali 300 mg, n=180 HCTZ 6.25* mg, n=194 HCTZ 12.5 mg, n=188 HCTZ 25 mg, n=173 ali 75*/HCTZ 6.25, n=187 ali 75*/HCTZ 12.5, n=189 ali 75*/HCTZ 25, n=186 ali 150/HCTZ 6.25, n=173 ali 150/HCTZ 12.5, n=184 ali 150/HCTZ 25, n=187 ali 300/HCTZ 12.5, n=180 ali 300/HCTZ 25, n=173 Placebo, n=192	**ali 150** vs Pbo: -2.01 mmHg, 95% CI [-3.63; -0.39], p=0.0152 **ali 300** vs Pbo: -3.33 mmHg, 95% CI [-4.95;-1.7], p<0.0001 **ali 150/HCTZ 6.25** :-3.42 mmHg (± 0.84), NS vs ali150 and NS vs H6.25 **ali 150/HCTZ 12.5** :-4.97 mmHg (± 0.83), p=0.0004 vs ali150 and p=0.0314 vs H12.5 **ali 150/HCTZ 25** :-5.71 mmHg (± 0.82), p<0.0001 vs ali150 and p=0.0001 vs H25 **ali 300/HCTZ 12.5** :-6.93 mmHg (± 0.83), p<0.0001 vs ali300 and p<0.0001 vs H12.5 **ali 300/HCTZ 25** :-7.33 mmHg (± 0.82), p<0.0001 vs ali300 and p<0.0001 vs H25	After 8 weeks' treatment: Significant reduction in DBP with aliskiren (RASILEZ) vs. placebo p<0.0002 Significant reduction in DBP with aliskiren (RASILEZ) /HCTZ vs. HCTZ and vs. RASILEZ only, with the exception of the combination aliskiren (RASILEZ) 150/HCTZ 6.25 mg.

2304	Phase III randomized, double-blind, controlled trial vs. **atenolol** (12 weeks) *Primary endpoint*: reduction in DBP ali 300 /ate 100 vs. each of the components in monotherapy	N= 690 (ITT) Mean age: 55 years mild to moderate hypertension	Ali group, n=230 Ate group, n=230 Ali/ate group, n=230	**ali/ate vs ali**: -2.88 mmHg (± 0.80), 95% CI [-4.46;-1.31], p<0.001 **ali/ate vs ate**: -0.49 mm Hg (± 0.80) 95% CI [-2.06; 1.09] NS	After 12 weeks' treatment: Significant reduction in DBP with aliskiren (RASILEZ) 300 mg/atenolol 100 mg vs. aliskiren (RASILEZ) 300 mg alone, p<0.001 No significant difference in the reduction of DBP with aliskiren (RASILEZ) /atenolol vs. atenolol alone.

* Aliskiren (Ali) 75 mg, off-label dose: the results will not be presented

**NB: in these trials, the breakdown of the doses did not take account of the patients' blood pressure status; this does not conform to the dose specified in the marketing authorization, which states that the doses can be increased and combinations considered in "inadequately controlled" patients.

Table 4 (page 2/2) "Summary of trials of Rasilez combined with another antihypertensive vs. antihypertensive alone"

Trial	Method	Patients	Treatment	Results	Conclusion
Trials vs. separate administration					
2305	Phase III randomized, double-blind, controlled trial of **ali/amlodipine** vs. **amlodipine** (6 weeks) *Primary endpoint*: reduction in DBP Ali 150/Amlo 5 mg vs. Amlo 5 mg alone	N= 541 (ITT) Mean age: 55 years mild to moderate hypertension	ali 150/Amlo 5, n= 187 amlo 5, n=177 amlo 10, n=177	amlo 5: -4.84 mmHg (± 0.62) amlo 10: -8.04 mmHg (± 0.62) ali 150/amlo 5: -8.46 mmHg (± 0.60) **ali 150/amlo 5 vs amlo 5** *Mean difference* : -3.62 mmHg (± 0.83), 95% CI [-5.25;-1.99], p<0.0001	After 6 weeks' treatment: Significant reduction in DBP with aliskiren (RASILEZ) 150 mg/amlodipine 5 mg vs. amlodipine 5 mg alone, p<0.0001
2307**	Phase III randomized, double-blind, controlled trial **ali/ramipril** vs. **ramipril** (8 weeks) *Primary endpoint*: reduction in DBP ali 300 /ram 10 mg vs. each of the components in monotherapy	N= 828 (ITT) Mean age: 60 years mild to moderate hypertension	ali 300/ram 10, n= 274 ali 300, n=279 ram 10, n=275	**ali 300/ram 10 vs ali 300** -1.46 mm Hg (± 0.72) 95% CI [-2.87;-0.05] p=0.0426 **ali 300/ram 10 vs ram 10** -2.07 mmHg (± 0.72) 95% CI [-3.49;-0.65], p=0.0043	After 8 weeks' treatment: Significant reduction in DBP with aliskiren (RASILEZ) 300/ramipril 10 mg vs. aliskiren (RASILEZ) 300 mg, p<0.05 Significant reduction in DBP with aliskiren (RASILEZ) 300/ramipril 10 mg vs. ramipril 10 mg, p<0.005
2327**	Phase III randomized, double-blind, controlled trial **ali/valsartan** vs. **valsartan**(8 weeks) *Primary endpoint*: reduction in DBP ali 300 /val 320 mg vs. each of the components in monotherapy	N= 1,776 (ITT) Mean age: 52 years mild to moderate hypertension	ali 300/Val 320, n= 438 ali 300, n=430 val 320, n=453 Pbo, n=455	**ali 300/val 320 vs ali 300** -3.15 (± 0.58) 95% CI [-4.29;-2.01], p<0.0001 **ali 300/val 320 vs val 320** -2.47 (± 0.57) 95% CI [-3.60;-1.35], p<0.0001	After 8 weeks' treatment: Significant reduction in DBP with aliskiren (RASILEZ) 300/valsartan 320 mg vs. aliskiren (RASILEZ) 300 mg, p<0.0001 Significant reduction in DBP with aliskiren (RASILEZ) 300/valsartan 320 mg vs. valsartan 320 mg, p<0.0001

**NB: in these trials, the breakdown of the doses did not take account of the patients' blood pressure status; this does not conform to the dose specified in the marketing authorization, which states that the doses can be increased and combinations considered in "inadequately controlled" patients