Open label study for the evaluation of the efficacy and safety of Fimasartan 60 mg alone as initial treatment and its randomized escalation to Fimasartan 120 mg or Fimasartan 60 mg/HCTZ 12.5 mg in Mexican patients with essential hypertension grades 1 or 2

Rationale and Methods

Introduction/Background:
Fimasartan (FMS) is an AT1 receptor antagonist with a very high affinity for its target indicated for once a day oral administration, it has been approved for the treatment of patients with essential hypertension in Korea and Mexico. Since the safety and efficacy of FMS were first demonstrated in Korean subjects only, the potential for ethnic factors to result in differing safety and efficacy in other populations needs to be addressed.

To assess the safety and efficacy of FMS 60-120 mg once a day alone or in a FDC with HCTZ 12.5 mg in the Mexican population, we conducted this 24 week study of a three step escalation treatment strategy (treat to a target DBP < 90 mmHg) of initial dosing with 60 mg Fimasartan QD, 120 mg Fimasartan once a day OR 60 mg Fimasartan + 12.5 mg HCTZ QD and 120 mg Fimasartan + 12.5 mg HCTZ QD in Mexican patients with essential hypertension grades 1-2.

Study Objectives:
1. To assess the efficacy of monotherapy with FMS 60 mg once a day in subjects with essential hypertension grades 1-2 after 8 weeks of therapy.
2. To assess and compare the efficacy of FMS 120 mg once a day and FMS 60 mg/HCTZ 12.5 mg once a day in subjects not responding to initial monotherapy.
3. To assess the efficacy of FMS 120 mg/HCTZ 12.5 mg once a day in subjects not responding to either FMA 120 mg once a day or FMS 60 mg/HCTZ 12.5 mg once a day at treatment week 12.
4. To assess the safety of both FMS monotherapy and combined treatment with FMS plus HCTZ.
5. To explore the effect of treatment with FMS 60 mg once a day on a series of pro-inflammatory and metabolic markers (hs-CRP, IL-6, ICAM-1, adiponectin, HOMA-S).
6. To explore the effect of FMS 60 mg on 24 hour, daytime and nighttime BP averages in a subset of participating subjects using ABPM.

Study Design:
This was a prospective, open, multicenter, 24 week study of initial monotherapy of subjects with essential hypertension grades 1-2 (90 mmHg ≤ DBP ≤ 109 mmHg) with FMS 60 mg QD during 8 weeks, followed by randomization of non-responders (DBP ≥ 90 mmHg) to FMS 120 mg or FMS 60 mg/HCTZ 12.5 mg QD and assignment to treatment with the FDC of FMS 120 mg/HCTZ 12.5 mg of non-responding randomized subjects at week 12. Responders at weeks 8 and 12 continued with their assigned treatment for their remaining study treatment period (Fig 1).
Subject selection. Consenting, 18-70 year old, male and female subjects with essential hypertension stages 1-2 (90 ≤ DBP ≤ 109 mmHg) were screened. Subjects with SBP ≥ 180 mmHg, secondary hypertension, significant renal or hepatic dysfunction, uncontrolled diabetes, BMI ≥ 40 kg/m², a history of a recent acute cardiovascular event or stroke, a history of autoimmune, connective tissue or significative active infectious diseases, or of hypersensitivity to or known contraindication for the use of ARBs or patients facing unacceptable risks according to the investigator’s judgement, as well as pregnant and breastfeeding mothers were not included.

Study interventions. FMS 60 mg during 8 weeks followed by either FMS 120 mg QD or the FDC of FMS 60 mg/HCTZ 12.5 mg QD; non-responding randomized subjects were finally assigned at Week 12 to treatment with the FDC of FMS 120 mg/HCTZ 12.5 mg once a day for the remaining 12 weeks of the total planned treatment period. Responders at weeks 8 and 12 continued their currently assigned treatment for the remaining 16 or 12 weeks of the treatment period.

Procedures. Subjects attended to sites every 4 weeks for the performance of study related assessments. In a subset of 11 subjects, 24 hour ABPM recordings were obtained using a validated device (Microlife WatchBP 03 (3MZ0) both at baseline and at week 8. Devices were set to register blood pressure measurements every 15 minutes during the day and every 30 minutes during the night. ECG recordings were obtained both at baseline and at week 24.

Data Analysis and Reporting:

Populations considered for analysis. Safety analysis was conducted on all subjects receiving at least one dose of study medication. Blood pressure (BP) changes from baseline and response rates were analyzed also on all subjects receiving at least one dose of the study medication (full data set, with multiple imputation). Exploratory analyses of changes from baseline pro-inflammatory and metabolic marker values were conducted on a complete case subject subset. ABPM analysis was conducted in a subset of 11 subjects with valid baseline and week 8 ABPM data.

Analysis and Reporting. Analysis was conducted using NCSS version 10.0 software. Baseline variables were summarized using descriptive statistical parameters as appropriate. Within group comparisons were performed with bilateral paired t-tests and between groups comparisons were conducted with bilateral student’s t or X² tests as applicable. The main response variable was the change from a reference point in time (i.e., baseline for subjects treated with FMS 60 mg QD, week 8 for subjects randomized to FMS 120 mg QD or FMS 60 mg/HCTZ 12.5 mg QD or week 12 for non responding subjects treated with FMS 120 mg/HCTZ 12.5 mg QD) as observed at weeks 8, 12 and 24 in subjects treated with FMS 60 mg QD, FMS 120 mg QD OR FMS 60 mg/HCTZ 12.5 mg QD and with FMS 120 mg QD, respectively. Response rates at weeks 8, 12 and 24 are presented for subjects treated with 60 mg QD, 60 mg/12.5 mg FMS/HCTZ or FMS 120 mg QD and subjects finally treated with 120 mg/12.5 mg FMS/HCTZ QD, respectively. In the subset of subjects with acceptable 24 hour baseline and week 8 ABPM assessments, 24 hour, daytime and nighttime DBP and SBP mean changes from baseline are also presented. For all within and between group comparisons, within/between group differences, together with their corresponding CI95 and bilateral p values are provided.

Ethical and Regulatory Considerations:

Ethics. An Independent Ethics Committe at each of the 13 participating sites reviewed and approved the study protocol and was in charge of the protection of the rights, safety and well-being of participating subjects along the study.

Regulatory considerations. The study was conducted in adherence with ICH-GCP and all applicable regulatory requirements under mexican law.

Quality control and quality assurance. Regular monitoring procedures to ensure adequate study conduction, and proper data generation, documentation and reporting was assigned to an Independent Contract Research Organization (Global ClinTrial, S.A. de C.V.), in addition, two high enrolling sites were also audited by Boryung Pharmaceutical Company Ltd. No observations or desviations were identified that may have put at risk both the subjects safety and well-being or data integrity.

Results

Baseline subject characteristics (n=272)

Subjects screened: 355
Subjects assigned to monotherapy: 272
Subjects randomized to FMS/HCTZ 60 mg/12.5 mg: 28
Subjects randomized to FMS 120 mg: 29
Subjects assigned to FMS/HCTZ 120 mg/12.5 mg: 12
Subjects withdrawn: 33
Adverse Event Related Withdrawals: 3
Serious Adverse Event Related Withdrawals: 1 (exacerbation of pre-existing closed angle glaucoma)
### Screened subjects (N= 355)

### Subjects enrolled (N= 272)

### Screening failures (N= 83, 23.38 %)
- Uncontrolled Diabetes mellitus (n= 33)
- DBP<90 mmHg (n= 16)
- Informed consent not granted or withdrawn (n= 15)
- Ineligible for washout (n= 6)
- Significant liver disease (n= 4)
- Screening post-end of screening period (n= 2)
- Autoimmune/Connective tissue disease (n= 1)
- Active systemic infection (n= 1)
- Significant systemic disease (n= 1)
- Grade 3 hypertension (n= 1)
- BMI ≥40 kg/m² (n= 1)
- Other (n= 2)

### Subjects withdrawn before completing 8 treatment weeks (N= 23.81 %)
- Lost to follow-up (n= 15)
- Informed consent withdrawn (n= 3)
- investigator decision (n= 1)
- Lack of treatment compliance (n= 1)
- Adverse event (n= 1, hypertensive emergency)
- Serious adverse event (n= 1, angioedema)

### Subjects assigned to Fimasartan 60 mg once a day (N= 191)

### Subjects assigned to Fimasartan 120 mg once a day (N= 29)

### Subjects assigned to Fimasartan/HCTZ 60 mg/12.5 mg once a day (N= 29)

### Subjects continuing with 60 mg Fimasartan once a day up to treatment week 12 (N= 188, 69 %)

### Subjects continuing with 120 mg Fimasartan once a day up to treatment week 12 (N= 29, 10.6 %)

### Subjects continuing with 60/12.5 mg Fimasartan/HCTZ once a day up to treatment week 12 (N= 28, 10.3 %)

### Subjects continuing with 60 mg Fimasartan once a day up to treatment week 12 (N= 188, 69 %)

### Subjects completing 24 treatment weeks with Fimasartan 60 mg/day (N= 183, 67.3 %)

### Subjects continuing up to treatment week 24 with 120 mg Fimasartan once a day (N= 20, 7.35 %)

### Subjects continuing up to treatment week 24 with 60/12.5 mg Fimasartan/HCTZ once a day (N= 24, 8.8 %)

### Subjects withdrawn between treatment weeks 8 &12 (N= 3, 1.1 %): 
- Ineligible DBP (n= 1)
- Consent withdrawal (n= 1)
- Lack of treatment adherence (n= 1)

### Subjects assigned to 120/12.5 mg FMS/HCTZ once a day at treatment week 12 (N= 12, 4.4 %) 
- 8 (2.94 %) from the 120 mg Fimasartan OD group
- 4 (1.47 %) from the 60/12.5 mg Fimasartan/HCTZ OD group

### Subject withdrawn between treatment weeks 8 and 12 (N= 1, 0.37 %): 
- Lack of treatment adherence (n= 1)

### Subjects completing 24 treatment weeks with Fimasartan 60 mg/day (N= 183, 67.3 %)

### Notes:
1. One subject with DBP>90 mmHg at treatment week 8 was not randomized by mistake and was maintained with 60 mg Fimasartan once a day during the rest of the subject’s participation in the study (subsequent DBP value <90 mmHg)
2. Two subjects with DBP< 90 mmHg at treatment week 8 were mistakenly assigned to 120 mg Fimasartan once a day and were kept on that dose level during the rest of their participation in the study
3. A subject with DBP<90 mmHg at treatment week 12 (Fimasartan/HCTZ 60/12.5 mg group) was mistakenly assigned to 120/12.5 mg FMS/HCTZ at treatment week 16.
This group of ethnically homogeneous (mestizos) subjects assigned to treatment comprise a wide variety of patients with essential hypertension and includes a high proportion of patients with concomitant risk factors (such as overweight, obesity, diabetes mellitus and dyslipidemia) that are highly prevalent in Mexico. This case mix, representative of the population of Mexican patients with essential hypertension, is also consistent with the recommendations issued by the ICH for the assessment of new antihypertensive drugs.

### Week 8 BP Change From Baseline (n= 272):

<table>
<thead>
<tr>
<th>Variable</th>
<th>Basal DBP (mmHg)</th>
<th>Basal SBP (mmHg)</th>
<th>Change from baseline (mmHg)</th>
<th>Change from baseline (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBP Mean ± SD</td>
<td>94.22 ± 4.37</td>
<td>150.85 ± 10.63</td>
<td>-11.27 ± 8.92</td>
<td>-16.03 ± 14.09</td>
</tr>
<tr>
<td>SBP Mean ± SD</td>
<td>82.95 ± 9.21</td>
<td>134.82 ± 16.21</td>
<td>-10.20, -12.33</td>
<td>-14.35, -17.72</td>
</tr>
<tr>
<td>p value*</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Bilateral Student t test

### Week 8 BP Response to Treatment (n= 272)

Treatment with 60 mg FMS once a day during 8 weeks resulted in clinically and statistically significant decreases of both the Diastolic and Systolic blood pressure values and in a high treatment response rate (75.4%).

### Pairwise treatment group comparison: FMS 120 mg QD vs. FMS/HCTZ 60 mg/12.5 mg

<table>
<thead>
<tr>
<th>BP Changes from week 8</th>
<th>Fimasartan 120 mg (n=29) Mean (SD)</th>
<th>Fimasartan/HCTZ 60 mg/12.5 mg (n=29) Mean (SD)</th>
<th>Mean difference (SD)</th>
<th>CI95 of the difference</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DBP Change from week 8</td>
<td>-8.28 (8.15)</td>
<td>-10.78 (7.37)</td>
<td>-2.50 (2.05)</td>
<td>-6.63, +1.62</td>
<td>0.22</td>
</tr>
<tr>
<td>SBP Change from week 8</td>
<td>-12.27 (12.50)</td>
<td>-16.77 (13.22)</td>
<td>-4.49 (3.40)</td>
<td>-11.32, +2.34</td>
<td>0.19</td>
</tr>
</tbody>
</table>

*Bilateral Student t test
Pairwise comparisons between subjects randomized to either FMS 120 mg QD or FMS/HCTZ 60 mg/12.5 mg QD were statistically non-significant.

**Week 24 BP Change From Week 12, Fimasartan/HCTZ 120 mg/12.5 mg QD (n= 12)**

<table>
<thead>
<tr>
<th>Week 12 DBP (mmHg) Mean ± SD</th>
<th>Week 24 DBP (mmHg) Mean ± SD</th>
<th>Change from week 12 (mmHg) Mean ± SD</th>
<th>CI95 of Change from Week 12</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>95.36± 7.21</td>
<td>84.55 ± 8.97</td>
<td>-10.82 ± 7.25</td>
<td>-3.95 -15.69</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Week 12 SBP (mmHg) Mean ± SD</th>
<th>Week 24 SBP (mmHg) Mean ± SD</th>
<th>Change from week 12 (mmHg) Mean ± SD</th>
<th>CI95 of Change from Week 12</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>153.90 ± 12.77</td>
<td>139.36 ± 13.84</td>
<td>-14.55 ± 10.62</td>
<td>-7.41 -21.68</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Bilateral, paired t test

Treatment with FMS/HCTZ 20 mg/12.5 mg QD in a small group of non responding subjects at week 12 resulted in clinically and statistically significant BP decrease, with a response rate of 75 %.
General response rate, defined as the achievement of a DBP<90 mmHg, increased as the planned treatment escalation was performed to a maximum of 96.32 % by week 24. Similarly, the proportion of subjects achieving both a DBP<90 mmHg and a SBP<140 mmHg increased progressively with treatment escalation to a maximum value of 87.13 % by week 24.

**Exploratory Analyses**

Changes observed for pro-inflammatory markers and insulin sensitivity were either non-significant (hs-CRP, IL-6, adiponektin, HOMA-IR) or with an uncertain clinical relevance (ICAM-1 change from baseline: +66.53 ng/mL, \(p<0.0001\)), given the variable direction and size of changes observed. Taken together, these results were considered as non-informative.

### Mean ABPM Week 8 Changes from Baseline (\(n=11\))

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Week 8</th>
<th>Change from baseline</th>
<th>Change from baseline CI95</th>
<th>(p) value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 hour mean DBP</td>
<td>80.62 (8.78)</td>
<td>74.79 (8.85)</td>
<td>-5.83 (6.67)</td>
<td>-10.31, -1.34</td>
<td>0.008</td>
</tr>
<tr>
<td>Daytime mean DBP</td>
<td>83.35 (2.52)</td>
<td>76.43 (9.64)</td>
<td>-6.91 (6.91)</td>
<td>-11.56, -2.27</td>
<td>0.003</td>
</tr>
<tr>
<td>Nighttime mean DBP</td>
<td>73.21 (11.03)</td>
<td>70.13 (8.52)</td>
<td>-3.07 (8.72)</td>
<td>-8.94, 2.78</td>
<td>0.13</td>
</tr>
<tr>
<td>24 hour mean SBP</td>
<td>136.69 (14.98)</td>
<td>123.99 (11.40)</td>
<td>-12.70 (14.66)</td>
<td>-22.54, -2.85</td>
<td>0.008</td>
</tr>
<tr>
<td>Daytime mean SBP</td>
<td>138.98 (14.40)</td>
<td>125.57 (12.58)</td>
<td>-13.41 (13.97)</td>
<td>-22.80, -4.03</td>
<td>0.005</td>
</tr>
<tr>
<td>Nighttime mean SBP</td>
<td>130.41 (18.95)</td>
<td>119.44 (11.88)</td>
<td>-10.97 (19.41)</td>
<td>-24.02, 2.07</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Treatment with Fimasartan 60 mg QD monotherapy resulted in significant mean decreases from baseline for both 24 hour and daytime systolic and diastolic blood pressure.
## Safety findings

### Summary of Treatment Emergent AEs

<table>
<thead>
<tr>
<th></th>
<th>FMS 60 mg QD</th>
<th>FMS 120 mg QD</th>
<th>FMS/HCTZ 60/12.5 mg QD</th>
<th>FMS/HCTZ 120 mg/12.5 mg QD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with AEs</td>
<td>57 (20.95 %)</td>
<td>3 (1.10 %)</td>
<td>6 (2.20 %)</td>
<td>2 (0.73 %)</td>
<td>64 (23.52 %)*</td>
</tr>
<tr>
<td>Number of AEs</td>
<td>108</td>
<td>9</td>
<td>8</td>
<td>7</td>
<td>132</td>
</tr>
<tr>
<td>Mild</td>
<td>70</td>
<td>7</td>
<td>4</td>
<td>4</td>
<td>85</td>
</tr>
<tr>
<td>Moderate</td>
<td>33</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>40</td>
</tr>
<tr>
<td>Severe</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Number of subjects with SAEs</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>3 (1.10 %)</td>
</tr>
</tbody>
</table>

*4 subjects reported adverse events during the initial treatment period (FMS 160 mg OP) and during their subsequence either with FMS 120 mg QD (subjects 1012-1019 y 105-008) or with FMS/HCTZ 120 mg QD (subjects 1012-1002 y 112-011)

A total of 132 adverse events were observed in 64/272 (23.52 %) study subjects. Eighty five of two hundred seventy two of which (64.39 %) were mild, 40/132 (30.30 %) were moderate and 7/132 (5.30 %) were severe (closed angle glaucoma exacerbation [1], epigastric pain [2], femoral fracture [1], increasing blood pressure [1], headache [1] and increasing liver enzymes [1]). By the end of the study 102 events (77.27 %) had been resolved while 30 (22.73 %) were continuing and subjects were lost for further follow-up. Three AEs were identified (closed angle glaucoma [1], bone fracture [2], all AEs were resolved with adequate medical treatment. None of these events was considered by the investigator as related with the study drug. No deaths were observed during the study.

### Summary of Related AEs

<table>
<thead>
<tr>
<th>System / Organ Class</th>
<th>Preferred term</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with any event, n (%)</td>
<td></td>
<td>25</td>
<td>9.19</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td></td>
<td>3</td>
<td>1.10</td>
</tr>
<tr>
<td>Epigastric pain</td>
<td></td>
<td>1</td>
<td>0.36</td>
</tr>
<tr>
<td>Increased hepatic enzymes</td>
<td></td>
<td>3</td>
<td>1.10</td>
</tr>
<tr>
<td>Central nervous system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td>10</td>
<td>3.67</td>
</tr>
<tr>
<td>Lipothymia</td>
<td></td>
<td>1</td>
<td>0.36</td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
<td>3</td>
<td>1.10</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensive emergency</td>
<td></td>
<td>1</td>
<td>0.36</td>
</tr>
<tr>
<td>Blood pressure increase</td>
<td></td>
<td>1</td>
<td>0.36</td>
</tr>
<tr>
<td>Hypotension</td>
<td></td>
<td>2</td>
<td>0.73</td>
</tr>
</tbody>
</table>
Conclusions

- Fimasartan at doses of 60 mg and 120 mg QD, either alone or in combination with HCTZ at doses of 12.5 mg produced clinically and statistically significant blood pressure decreases in Mexican subjects with essential hypertension.

- A treatment to goal (DBP< 90 mmHg) strategy starting with Fimasartan 60 mg QD and continuing with either Fimasartan 120 mg QD or FMS/HCTZ 60/12.5 mg QD, with a final escalation to FMS/HCTZ 120/12.5 mg QD resulted in a high response rate (96.32 %) in this sample of mild to moderate essential hypertension patients.

- In comparison with FMS 120 mg QD, FMS/HCTZ 60/12.5 mg QD resulted in larger blood pressure decreases from the reference value, probably as a result of a small sample size for this comparison the difference was, however, non significant.

- Fimasartan's safety profile appears to be very similar to that of other agents of this drug class.

- Fimasartan proved to be safe and efficacious as an alternative treatment for Mexican patients with mild to moderate essential hypertension.

Disclosures

*Head of the Physiology Department of the Centro Universitario de Ciencias de la Salud de la Universidad de Guadalajara, Guadalajara, Jalisco, México and receives personal fees for clinical research, consulting and lecturing services rendered to Específicos Stendhal S.A. de C.V. , Novartis Pharmaceutical, Merck Sharp & Dohme, Boehringer Ingelheim, NovoNordisk, Amgen INC, Aventis Pharma and Bayer de México S.A . de C.V.

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