Hypertension Research (2017) 40, 472–476

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ORIGINAL ARTICLE

Long-term (52-week) safety and efficacy of Sacubitril/valsartan in Asian patients with hypertension

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Sacubitril/valsartan (LCZ696), a first-in-class angiotensin receptor-neprilysin inhibitor, demonstrated significant reductions in office and 24 h ambulatory blood pressure (BP) over 8 weeks in Asian patients with hypertension. This 52-week extension to the 8-week core study was aimed at evaluating the long-term safety, tolerability and efficacy of sacubitril/valsartan. Patients who completed an 8-week randomized study (the core study) were enrolled in this 52-week open-label study and received sacubitril/valsartan 200 mg QD. The sacubitril/valsartan dose was uptitrated to 400 mg QD if BP was uncontrolled (>140/90 mm Hg) after 4 weeks. Subsequently, in patients with uncontrolled BP, treatment was intensified every 4 weeks with amlodipine 5–10 mg followed by hydrochlorothiazide 6.25–25 mg. Of the 341 patients enrolled, 7 (2.1%) discontinued the study drug due to adverse events (AEs). The incidence of AEs and serious AEs were 63.9 and 3.8%, respectively, and no deaths were reported in this study. The most frequent AEs were nasopharyngitis (18.2%) and dizziness (8.8%). Events that were potentially indicative of low BP were infrequent. One patient reported mild transient angioedema (lasting 2.5 h) that resolved without treatment but led to study drug discontinuation. The sacubitril/valsartan-based regimen provided clinically significant mean sitting systolic BP (msSBP) and mean sitting diastolic BP (msDBP) reductions from baseline (–24.7/–16.2 mm Hg). The overall BP control, msSBP and msDBP response rates were 75.3, 90.6 and 87.6%, respectively. Long-term use of sacubitril/valsartan was generally safe and well-tolerated in patients with hypertension and provided significant BP reductions from baseline.
Hypertension Research (2017) **40,** 472–476; doi:10.1038/hr.2016.151; published online 17 November 2016

Keywords: efficacy; long-term; sacubitril/valsartan; safety

INTRODUCTION

Hypertension is currently recognized as a major global public health challenge and is associated with high mortality and morbidity.[1–3] The prevalence of hypertension in Asian countries is similar to that in developed countries, and is rapidly rising owing to the increasing elderly population, increased incidence of obesity and unhealthy dietary habits such as excessive salt intake.[4] The currently used antihypertensive therapies in Asian countries include calcium-channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers and diuretics.[5] However, these classes of drugs have demonstrated varying degrees of success in achieving target blood pressure (BP) values in hypertensive patients.[5,6] Thus, suboptimal treatment and difficulties in achieving guideline-recommended target BP goals emphasize the need for a new class of drugs.

Natriuretic peptides have potent natriuretic and diuretic properties, which help in regulating sodium and water homeostasis, and lower vascular tone and BP, thereby providing cardiovascular and renal protection.[7] As natriuretic peptides are primarily degraded by neprilysin, the inhibition of neprilysin was investigated as a therapeutic strategy to increase natriuretic peptide levels.[8] However, neprilysin inhibition concomitantly increases the levels of vasopressor peptides such as angiotensin II and endothelin, which limits the therapeutic benefits that neprilysin inhibitors could provide as stand-alone antihypertensive agents.[7,8] Therefore, the simultaneous inhibition of neprilysin and the renin-angiotensin-aldosterone system might prove beneficial in achieving BP control.

Sacubitril/valsartan (LCZ696) is a first-in-class angiotensin receptor-neprilysin inhibitor that provides neprilysin inhibition, and angiotensin receptor blockade via its sacubitril (AHU377) and valsartan components, respectively, and thereby can reduce BP and offer cardioprotective benefits.[9,10] Previous clinical studies in predominantly Caucasian patients with hypertension have shown that sacubitril/valsartan significantly reduced BP and was generally safe and well-tolerated.[11] In the 8-week dose-ranging study in Asian patients with hypertension, sacubitril/valsartan demonstrated similar

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Received 24 June 2016; accepted 6 September 2016; published online 17 November 2016

reductions in office and 24-h ambulatory BP and was well-tolerated.[10] The current study was a 52-week extension to the 8-week core study and is the first study to assess the long-term safety, tolerability and efficacy of sacubitril/valsartan in patients with essential hypertension.

METHODS

Study design and participants

This study was a 52-week, outpatient, multicenter (China, Japan, Korea, Taiwan and Thailand), open-label, single-arm extension to an 8-week, double-blind, dose-finding study (the core study) in patients with essential hypertension (mean sitting systolic BP (msSBP) $\geqslant$ 140 and $<$180 mm Hg; mean sitting diastolic BP (msDBP) $\geqslant$ 95 and $<$110 mm Hg). Male and female Asian adults with mild-to-moderate essential hypertension, who had completed all of the core study-related procedures, and were able to communicate and comply with the present study requirements and medications, were enrolled in this extension study.[10] Eligible patients were administered sacubitril/valsartan 200 mg QD, irrespective of the treatment received in the core study (sacubitril/valsartan 100, 200 or 400 mg QD, or placebo) after providing written informed consent. The LCZ696 dose was uptitrated to 400 mg QD, if BP was uncontrolled ($>$140/90 mm Hg) after 4 weeks. Downtitration to 100 mg QD was allowed if hypotensive symptoms developed. If patients still remained inadequately controlled on sacubitril/valsartan 400 mg for at least 4 weeks, the treatment was intensified by adding amlodipine 5 mg. The dose of amlodipine could be titrated up to 10 mg, followed by the addition of hydrochlorothiazide (HCTZ) starting at daily doses of 6.25 mg and titrating up to 25 mg as appropriate according to local country regulations (Figure 1).

The study protocol and sample informed consent form were reviewed and approved by an institutional review board/independent ethics committee/research ethics board prior to study initiation. The study was performed in accordance with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines for Good Clinical Practice, applicable local regulations (including the European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare) and ethical principles of the Declaration of Helsinki.

Study assessments

Safety. The safety assessments included the recording of all adverse events (AEs) and serious AEs (SAEs), and their severity and relationship to the study drug. Laboratory evaluations included hematology, clinical chemistry and urinalysis. Blood samples for the laboratory evaluations, as well as for sodium, potassium, creatinine and blood urea nitrogen measurements, were collected at regular intervals. Regular assessments of vital signs, physical condition and body weight were performed.

An external data-monitoring committee independent of Novartis was appointed to review the incidence of pre-specified clinical AEs including angioedema and SAEs. Angioedema and angioedema-like AEs were adjudicated by an Angioedema Adjudication Committee.

Efficacy. Changes in clinic BP values (msSBP, msDBP and mean sitting pulse pressure (msPP) (msSBP – msDBP)) from baseline (week 0 of the core study) to the end of the 52-week extension study were measured to assess BP control, SBP response and DBP response. The BP control was defined as msSBP $<$ 140 mm Hg and msDBP $<$ 90 mm Hg and, SBP response as msSBP $<$ 140 or $\geqslant$ 20 mm Hg reduction from baseline and DBP response as msDBP $<$ 90 or $\geqslant$ 10 mm Hg reduction from baseline. Arterial BP was measured using an automated BP device (such as the Omron BP monitor) in accordance with the British Hypertension Society 2004 guidelines for hypertension management.[12] Sitting and standing BP measurements were performed at trough (23–26 h post-morning dose) at the time of screening and at all subsequent visits through the end of the study. BP was measured in the same arm used in the core study. Four separate sitting BP readings were obtained after resting for 5 min in the sitting position, with 2-min intervals between measurements and with the cuff fully deflated between measurements. One standing BP measurement was taken for safety analysis after the patient stood for 2 min. The mean of the last three sitting BP measurements and the single standing measurement were recorded and documented.

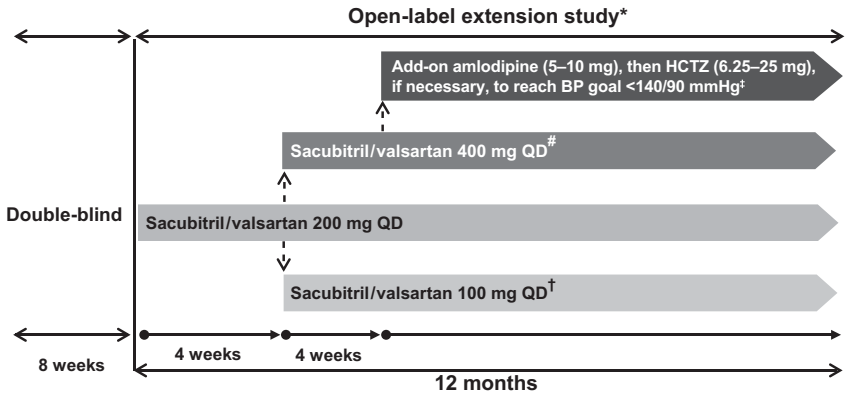
Sample size estimation

The current ICH Principles for Clinical Evaluation of New Antihypertensive Drugs guidelines recommend a total exposure of 6 months for at least 300 patients and 12 months for 100 patients to assess the long-term safety of an antihypertensive agent. Assuming a discontinuation rate of 12%, a sample size of 344 enrolled patients was planned for this long-term, open-label, extension study.

Statistical analyses

Safety and efficacy analyses were performed on all patients who consented to participate in the extension study and had received at least one dose of the study medication (the 'treated' set). The assessment of safety and tolerability was based primarily on the frequency of AEs, laboratory data including abnormalities, SAEs including deaths, AEs assessed by the investigators as related to study medication, as well as vital signs including BP measurements.

The assessment of efficacy was based on the changes in msSBP/msDBP from baseline to the end of the extension study. In addition, summary statistics for



*An open-label extension to an 8-week, double-blind, dose-finding study conducted in China, Japan, Korea, Taiwan, and Thailand
#If msSBP ≥140 mm Hg or msDBP ≥90 mm Hg, LCZ696 dose was up-titrated
†If a patient experienced hypotension (msSBP <100 mm Hg and/or msDBP <55 mm Hg) or symptoms of hypotension, LCZ696 dose was down-titrated
‡If msSBP >140 mm Hg or msDBP >90 mm Hg at any visit after 4 weeks of LCZ696 up-titration to 400 mg, amlodipine (5–10 mg), then HCTZ (6.25–25 mg), if necessary, was added to achieve the BP target
BP, blood pressure; HCTZ, hydrochlorothiazide; msDBP, mean sitting diastolic blood pressure; msSBP, mean sitting systolic blood pressure

Figure 1 Study design.

the proportion of patients who achieved BP control were presented by maximum-extension treatment group for the 'treated' set.

RESULTS

Patient disposition

Of the 341 patients enrolled in this extension study, 320 (93.8%) completed the study. The most common reasons for study discontinuation were withdrawal of consent (8 (2.3%)) and AEs (7 (2.1%); Figure 2).

Demographics and baseline characteristics are presented in Table 1. All patients were of Asian origin (46% were Japanese) and the majority were men (71%). The mean age of patient was 51.8 years and ~11% ($n=37$) of patients were aged ⩾65 years. The overall baseline msSBP, msDBP and msPP values were 154.4, 99.7 and 54.7 mm Hg, respectively. However, the patients who required add-on therapy had higher baseline BP values, especially for msSBP and msPP.

Patient exposure

The mean duration of sacubitril/valsartan exposure for all patients was 343.8 days. A total of 327 and 144 patients were exposed to sacubitril/valsartan for at least 180 and 360 days, respectively. All 341 patients received at least 1 dose of the study medication; 340 patients began the study treatment with sacubitril/valsartan 200 mg and one patient received sacubitril/valsartan 200 mg/amlodipine for 1 day prior to study discontinuation. Twelve patients were downtitrated to sacubitril/valsartan 100 mg QD and 201 patients were uptitrated to sacubitril/valsartan 400 mg QD. The majority of patients (228 (66.9%)) remained on sacubitril/valsartan monotherapy until study end. Patients who needed treatment intensification (109 (31.96%)) mostly received amlodipine and only 4 patients received both amlodipine and HCTZ.

Safety

The incidence of AEs reported in ⩾2% of patients during the extension period is presented in Table 2. Most AEs were mild or moderate in severity. The most frequently reported AEs were nasopharyngitis (18.2%) followed by dizziness (8.8%). However, neither of these was serious or resulted in discontinuation of the study drug. One patient had an upper respiratory tract infection, which was severe in intensity. Other AEs that could potentially indicate low BP included hypotension (1.5%), syncope (0.9%), pre-syncope (0.3%) and postural dizziness (0.3%). Mild angioedema was reported for one patient during the extension study. The event lasted 2.5 h and resolved without treatment. However, this event resulted in discontinuation of the study drug.

SAEs were reported in 13 (3.8%) patients. Two patients had SAEs that led to discontinuation of the study drug (one patient had syncope and the other had cerebral infarction). No deaths were reported during the study.

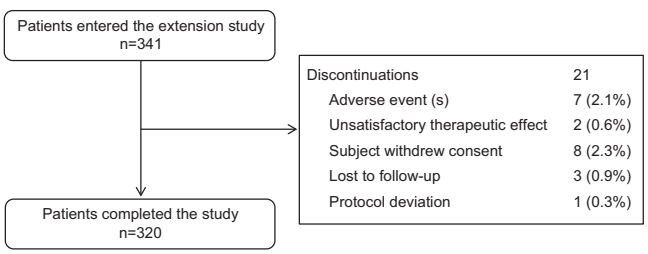


Figure 2 Patient disposition.

Discontinuation of the study drug due to AEs was reported for 7 (2.1%) patients, of which 2 were due to SAEs and 5 due to non-SAEs.

Laboratory evaluations

Laboratory findings were generally unremarkable. A total of 9 (2.6%) patients had low serum potassium levels (<3.5 mmol l^{-1}); however, the values returned to normal for 6 patients at subsequent visits. An increase in serum potassium levels (>5.5 mmol l^{-1}) was observed in 3 (0.9%) patients, and these returned to normal at subsequent visits. No patients had an increase in serum potassium levels ⩾6 mmol l^{-1} (Table 3).

Efficacy

The 52-week treatment with sacubitril/valsartan with or without the addition of amlodipine and HCTZ provided clinically significant reductions in msSBP (−24.7 mm Hg), msDBP (−16.2 mm Hg) and msPP −8.5 mm Hg from baseline (Figure 3a). The BP reduction was maintained throughout the 52-week treatment period. The msSBP and msDBP values over the course of 52 weeks are presented by visit in Figures 3b and c, respectively. At endpoint, the overall proportion of patients with adequate BP control was 75.3%. Similarly, the SBP and DBP response rates at endpoint were 87.6 and 90.6%, respectively (Figure 4).

DISCUSSION

This 52-week extension study primarily assessed the long-term safety and tolerability of sacubitril/valsartan in adult Asian patients with essential hypertension. The study results indicate that long-term treatment with sacubitril/valsartan is generally safe and well-tolerated. The most commonly reported AE was nasopharyngitis. Incidence of mild angioedema was reported in one patient that lasted 2.5 h and resolved without any intervention. The laboratory findings were mostly unremarkable. The incidence of SAEs was low and no deaths were reported in this study.

Table 1 Demographics and baseline characteristics (treated set)

Parameter	N = *341*
Age, years	51.8 ± 9.73
Age group, n *(%)*	
<65 years	304 (89.1)
⩾65 years	37 (10.9)
Gender, male, *n* (%)	242 (71.0)
Race, Asian, *n* (%)	341 (100)
Ethnicity, n *(%)*	
Japanese	157 (46.0)
Chinese	75 (22.0)
Korean	35 (10.3)
Taiwanese	40 (11.7)
Thai	34 (10.0)
Duration of hypertension, years	5.8 ± 6.04
msDBP, mm Hg	99.7 ± 3.82
msSBP, mm Hg	154.4 ± 9.56
msPP, mm Hg	54.7 ± 9.03

Abbreviations: msDBP, mean sitting diastolic blood pressure; msPP, mean sitting pulse pressure; msSBP, mean sitting systolic blood pressure.
Data are presented as mean ± s.d., unless specified.

Table 2 Incidence of adverse events (⩾2%) and serious adverse events during the extension period (treated set)

Adverse events	N = *341*
Any AE; n *(%)*	*218 (63.9)*
Nasopharyngitis	62 (18.2)
Dizziness	30 (8.8)
URTI	26 (7.6)
Headache	11 (3.2)
Cough	9 (2.6)
Hematuria	8 (2.3)
Hyperuricemia	8 (2.3)
Pharyngitis	8 (2.3)
Dyspepsia	7 (2.1)
Hyperlipidemia	7 (2.1)
Insomnia	7 (2.1)
Palpitations	7 (2.1)
Rhinitis allergic	7 (2.1)
Any SAE; n *(%)*	*13 (3.8)*
Appendicitis	2 (0.6)
Syncope	2 (0.6)
Acute myocardial infarction	1 (0.3)
Bile duct stone	1 (0.3)
Bronchitis	1 (0.3)
Cerebral infarction	1 (0.3)
Cholangitis acute	1 (0.3)
Cholecystitis	1 (0.3)
Emphysema	1 (0.3)
Gastroenteritis	1 (0.3)
Intervertebral disc protrusion	1 (0.3)
Nasal septum deviation	1 (0.3)
Pneumonia	1 (0.3)
Pneumothorax	1 (0.3)
Pulmonary hemorrhage	1 (0.3)
Renal cancer	1 (0.3)

Abbreviations: AE, adverse event; SAE, serious adverse event; URTI, upper respiratory tract infection.

Table 3 Laboratory evaluations (treated set)

Biochemistry	N = *341*
Potassium, mmol l^{-1}; n *(%)*	
⩾6.0	0 (0.0)
>5.5	3 (0.9)
<3.5	9 (2.6)
BUN (>14.28 mmol l^{-1})	1 (0.3)
Creatinine (>176.8 μmol l^{-1})	1 (0.3)
Sodium (<130 mmol l^{-1})	0 (0.0)

Abbreviation: BUN, blood urea nitrogen.

The safety profile of sacubitril/valsartan in this long-term extension study was comparable to the 8-week core study, except for an increased incidence of dizziness.[10] Nasopharyngitis was the most frequently reported AE and its incidence was similar to that of patients who received sacubitril/valsartan 200 and 400 mg in the core study.[10] The incidence of dizziness was higher in this study (8.8%) compared with the core study. However, most dizziness events in this long-term study were mild or moderate in severity and none of the events led to discontinuation of the study drug. The sacubitril/valsartan safety profile in this long-term study was also comparable to that reported in the 8-week, multinational study in Caucasian patients with hypertension.[11]

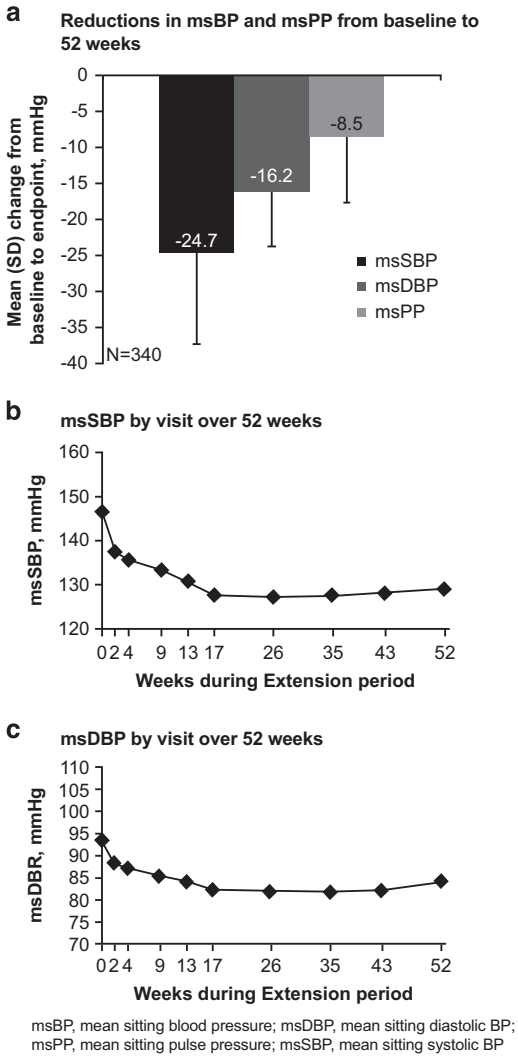
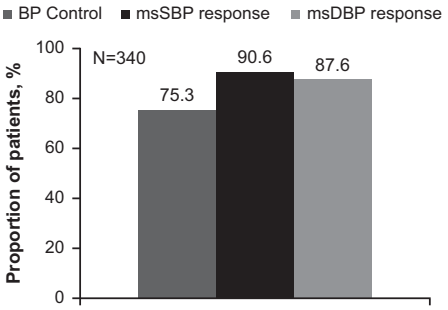


Figure 3 Changes in mean sitting blood pressure with a sacubitril/valsartan-based regimen. (**a**) Reductions in msBP and msPP from baseline to 52 weeks, (**b**) msSBP by visit over 52 weeks, (**c**) msDBP by visit over 52 weeks.

Regarding sacubitril/valsartan efficacy, previous trials in hypertension have shown that an 8-week treatment course produced greater reductions in BP compared with placebo in the Asian patient with hypertension population[10] and with valsartan in the Caucasian population.[11] In this long-term study, patients who needed add-on treatment had a higher baseline BP values, especially msSBP and msPP; however, the majority of the patients remained on sacubitril/valsartan monotherapy. Clinically significant reductions in msSBP, msDBP and msPP were observed with the sacubitril/valsartan-based regimen, with the majority of patients achieving the target BP control, and msSBP and msDBP responses.

Recently, the Sytolic Blood Pressure Intervention trial (SPRINT) trial emphasized on the importance of lowering SBP to a lower target (120 mm Hg) in reducing the risk of fatal and non-fatal cardiovascular events in patients with mild-to-moderate hypertension, and high cardiovascular risk without diabetes.[13] However, even the higher BP



BP control, msSBP <140 mm Hg and msDBP <90 mm Hg;
SBP response, msSBP <140 mm Hg or ≥20 mm Hg reduction from baseline; DBP response, msDBP <90 mm Hg or ≥10 mm Hg reduction from baseline
BP, blood pressure; DBP, diastolic blood pressure; msDBP, mean sitting DBP; msSBP, mean sitting SBP; SBP, systolic blood pressure

Figure 4 Blood pressure control, and msSBP and msDBP responses with a sacubitril/valsartan-based regimen.

target, $<140/90$ mm Hg, is achieved only in 50% of the population in the US alone, suggesting the challenges in achieving BP control.[14] In this study, sacubitril/valsartan with or without amlodipine and HCTZ showed effective SBP lowering with an SBP response rate of 90.6%.

The major limitations of this extension study were the lack of an active comparator and the open-label study design. However, PARAMETER is the first randomized study that showed superior efficacy of sacubitril/valsartan 400 mg QD compared with the angiotensin receptor blocker, olmesartan 40 mg QD in lowering the central aortic systolic pressure and central pulse pressure in elderly patients with systolic hypertension and increased pulse pressure, in both short and long-term (12 and 52 weeks).[15] Moreover, in another study that evaluated the safety and efficacy of sacubitril/valsartan in chronic heart failure patients (PARADIGM-HF) with a double-blind randomized treatment period, that lasted up to 51 months (median 27 months), sacubitril/valsartan was safe and well-tolerated with greater benefit in reducing risk of CV death, all-cause mortality and hospitalization for heart failure in addition to decreasing the symptoms and physical limitations of heart failure compared with an ACE inhibitor enalapril.[16]

In conclusion, this long-term (52-week) extension study showed that sacubitril/valsartan, a first-in-class angiotensin receptor-neprilysin inhibitor, is generally safe and well-tolerated and produces sustained BP reduction in Asian patients with essential hypertension.

CONFLICT OF INTEREST

Kazuomi Kario recieved research grants from Novartis Pharma K.K., Teijin Pharma, Takeda Pharmaceutical, Omron Healthcare and Fukuda Denshi, and honoraria from Mochida Pharmaceutical, Takeda Pharmaceutical, Daiichi-Sankyo and Sumitomo Dainippon Pharma. Kudsia Hafeez and Jack Zhang are employees of Novartis. The remaining authors declare no conflict of interest.

ACKNOWLEDGEMENTS

The study was sponsored by Novartis Pharma AG, Basel, Switzerland. Ying Zhang was previously employed by Novartis and contributed to the statistical analysis of the study. We thank Vennila Dharman (Novartis Healthcare Pvt Ltd, India) for providing medical writing support. This study was supported by Novartis Pharma AG, Basel, Switzerland. ClinicalTrials.gov Identifier: NCT01256411.

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