

# In vitro and in vivo postmarketing surveillance of valsartan, alone or in combination with amlodipine or hydrochlorothiazide, among Palestinian hypertensive patients

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**Objectives:** The objectives of this study were to evaluate the general quality of the most prescribed products of valsartan (VL; alone or in combination) and to evaluate their efficacy and safety among Palestinian population through in vivo postmarketing surveillance.

**Patients and methods:** The first part was pharmacopeial quality control assay, including dissolution, disintegration, friability, and weight uniformity for VL. The second part was a 3-month cardiology clinics, observational, postmarketing surveillance pilot study that included 103 hypertensive patients who were prescribed 80 mg or 160 mg of VL as monotherapy or combination therapy. The end points were reduction in blood pressure (BP) and the rate of incidence of adverse effects (AEs) at weeks 4 and 8.

**Results:** According to our quality control tests, all VL products showed high-quality standards according to the international guidelines. A reduction in BP was observed at weeks 4 and 8, and no significant difference was observed between the strengths of 80 mg and 160 mg. Higher BP reduction was observed after the use of combination therapy. Moreover, VL was well tolerated; most of the AEs were of mild-to-moderate intensity. In general, the most frequently reported AEs included headache (17.5%), dizziness (11.75%), and weakness (11.7%). No serious AEs or death cases were reported during the study period.

**Conclusion:** High quality of VL tablet products was used; hence, the observed efficacy and safety results should be related to patient's factors and not due to any product defects or sub-standard quality. Moreover, VL is an effective treatment for essential hypertension.

**Keywords:** valsartan, quality control, postmarketing, surveillance, Palestine

## Introduction

Valsartan (VL) is a nonpeptide angiotensin receptor blocker (ARB) used orally for the treatment of high blood pressure (BP).<sup>1</sup> It inhibits the angiotensin type 2 receptor that is responsible for the decrease in aldosterone secretion. This causes an arteriolar and venous dilation, resulting in a decrease in BP.<sup>1</sup> Accordingly, this drug has been approved for the initial treatment of primary BP worldwide.<sup>2,3</sup>

In fact, the European Society of Hypertension/European Society of Cardiology has included this medication as a first-line therapy in patients with high BP.<sup>4</sup> VL is available in several strengths, 40 mg, 80 mg, 160 mg, and 320 mg, in order to meet the needs of patients.<sup>5</sup>

However, 80 mg and 160 mg are the only strengths available in Palestine. These two strengths are available as monotherapy or in combination therapy with other

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antihypertensive agents such as hydrochlorothiazide (HCT) and amlodipine (AML; Table 1).<sup>6</sup>

The efficacy of VL is independent of age and sex, but may depend to a certain extent on ethnic origin, since Afro-American patients are less sensitive to ARBs than Caucasians.<sup>7</sup>

Unlike angiotensin-converting enzyme inhibitors, ARBs are relatively well tolerated and do not induce cough. ARBs are indicated in mild, moderate, and severe essential high BP, where their efficacy has been proven in many studies.<sup>7-9</sup>

Moreover, VL has a very low incidence of side effects, approximately similar to that of placebo, with an acceptable overall safety profile.<sup>4,6</sup> Biswas et al<sup>10</sup> have assessed several adverse effects (AEs), including dizziness, diarrhea, headache, palpitation, nausea/vomiting, rash, sweating, cough, dyspepsia, dyspnea, epistaxis, and malaise, as suspected adverse drug reactions among patients under VL treatment. Dizziness, headache, and fatigue were commonly reported in patients who used this drug; the most common reason that led to stop the use of VL was dizziness.

In fact, in another study conducted on Taiwanese population, the incidence rate of dizziness as AE was ~3.58% and 4.33% using VL alone and in combination with other antihypertensive drugs, respectively.<sup>11</sup> It was also found that the incidence of dizziness increased by increasing the dose.<sup>12</sup> Therefore, it was suggested that ARBs should be initially started in low doses and then increased according to their efficacy and safety in order to minimize dizziness.<sup>13</sup> Other AEs have been also reported such as headache (1.04% in monotherapy vs 1.44% in combination), cough (1.04% in monotherapy vs 0.76% in combination), and constipation (1.04% in monotherapy vs 0.76% in combination).<sup>11</sup>

Several in vivo postmarketing surveillance studies are usually conducted on marketed drugs in order to assess the efficacy and safety of these drugs.<sup>11,14,15</sup>

However, these studies are costly and time consuming since they need years and involve the contribution of several physicians, clinical institutions, and patients. Therefore, in vitro postmarketing surveillance, which involves pharmacopeial and technological quality control (QC) assessment of drug products, may be used as a quick and cheap alternative to the in vivo surveillance studies.<sup>16,17</sup>

To the best of our knowledge, there are neither in vitro nor in vivo postmarketing studies about VL in Arab countries. Accordingly, the objectives of this study were to evaluate the pharmacopeial QC of the most prescribed products of VL alone or in combination with other drugs. Moreover, a pilot

**Table 1** VL tablet products (alone or in combination) available on the Palestinian pharmaceutical market

Strength/ tablet	VL		VL/HCT			VL/AML				
	Diovan® (Novartis)	Valzan® (Pharmacare)	Vector® (Unipharm)	Co-diovan® (Novartis)	Valzan-HCT® (Pharmacare)	Valuzid® (Jerusalem Pharm)	Vector plus® (Unipharm)	Atrusar® (Birzeit)	Exforge® (Novartis)	Valzadepin® (Pharmacare)
80 mg	A	A	A	A	A	A	NA	A	A	A
160 mg	A	A	A	A	A	A	A	A	A	A

**Note:** A means available on the Palestinian pharmaceutical market and NA means not available on the Palestinian pharmaceutical market.  
**Abbreviations:** VL, valsartan; HCT, hydrochlorothiazide; AML, amlodipine.

study was used in order to evaluate the efficacy and safety of VL alone or in combination with other antihypertensive agents among Palestinian population through in vivo postmarketing surveillance.

## Patients and methods

### Postmarketing surveillance study

#### In vivo postmarketing surveillance study

##### Study design

This was a 3-month cardiology clinics, observational, post-marketing surveillance pilot study designed and approved by the local ethics committee (Institutional Review Board [IRB] of An-Najah National University). In this contest, the primary objective was to evaluate the efficacy of VL as mono- or combination therapy among Palestinian patients with high BP. The secondary objective was to assess the incidence rate of side effects that appeared during the use of VL as mono-therapy or combination with other antihypertensive drugs.

##### Patients

Participants aged >20 years and diagnosed with high BP (sitting diastolic BP [DBP] >90 mmHg and/or systolic BP [SBP] >140 mmHg) were included in the study. Patients with severe medical conditions, using any other investigational drugs at the time of study, or with known hypersensitivity to VL or any component in the formulation; breastfeeding or pregnant women; or patients with a history of any malignancy within the previous 5 years were excluded from the study. All participants signed a written informed consent, and the protocol was in accordance with the ethical principles laid down in the Declaration of Helsinki.

##### Treatment and assessment

At the first visit (week 0), several information were recorded from the patients, including their sociodemographic data, medical history, and used medications. BP was measured by the physician according to his discernment; the patients were prescribed VL as a monotherapy or in combination. At the following visit (week 4), the patient's BP, medication changes, and AEs were recorded. Similar evaluation was done at the final visit (week 8).

The incidence rate of side effects of VL alone or in combination therapy was assessed according to the patient's answer to our standard question: "Did you feel or sense any of the following side effects?"

Moreover, the efficacy of VL on BP was assessed by measuring the mean change between weeks 0, 4, and 8, and the reduction in BP was calculated.

##### Statistical analyses

All statistical analyses were performed using the SPSS 16 software package (SPSS Inc., Chicago, IL, USA). Categorical variables were expressed as frequencies and percentages. Numerical variables that did not follow a normal distribution were represented as median and interquartile range. Categorical variables were compared by Fisher's exact test when the expected frequency was  $\leq 5$ . Two-sample comparisons were carried out by the Mann-Whitney *U*-test for nonnormally distributed variables. Numerical variables were tested for normal distribution with the Kolmogorov-Smirnov test. *P*-values <0.05 were considered statistically significant.

## In vitro postmarketing QC

### Materials and methods

#### Formulations

Ten different brands of VL (alone and in combination) were available in the Palestinian market as shown in Table 1; however, actually only six brands were studied because these were the most prescribed for high BP in the clinic during the study period. These brands were subjected to visual and pharmacopeial inspection according to the United States Pharmacopoeia 38 (USP 38)/National Formulary 33.<sup>18</sup>

#### Chemicals and reagents

USP VL, HCT, and AML besylate reference standards (RIs; Holland Moran, Holon, Israel) were used. Valzan 160 mg tablets, valzan-HCT (160/25), and valzadepin (10/160) were obtained from Pharmacare PLC (Ramallah, Palestine).

High-performance liquid chromatography (HPLC)-grade solvents such as acetonitrile and methanol were purchased from EMD Millipore (Billerica, MA, USA) and were used as received. Potassium dihydrogen phosphate, sodium hydroxide pellets, trifluoroacetic acid, triethylamine, phosphoric acid, and glacial acetic acid were also purchased from EMD Millipore. High purified water was prepared by using a EMD Millipore Milli-Q plus water purification system. All other reagents were of analytical grade.

#### Instruments and chromatographic conditions

The HPLC system consisted of LaChrom (Merck-Hitachi, Kent, England) equipped with model L-7100 pump, L-7200 autosampler, L-7300 column oven, DAD L-7450 photodiode array detector, and D-7000 software HSM Version 3.1 (Merck-Hitachi).

The HPLC experimental conditions were optimized on octadecyl silane C18 chemically bonded column (125×3.0 mm id, 5 μm particles) that was purchased from

ACE (London, UK). Weights were measured using Ohaus balance (Model DV215CD; Shekel Ltd, Israel); pH was identified using Toledo GmbH pH meter (Model S47-K; Agentek, Mettler Toledo, Switzerland).

## Method

All VL tablet products available in the Palestinian pharmaceutical market were reported and assessed for their price. However, only products that were prescribed in the post-marketing surveillance were subjected to complete in vitro QC. Accordingly, visual examination was used to assess the general look and appearance of these tablet products. The assay of VL alone or in combination with other drugs was assessed according to the procedure reported in the related reference (Table 2).

For weight uniformity test, 20 tablets from each of the six products of VL were weighed individually using an analytical weighing balance. The percentage relative standard deviation and the average weights for each product were calculated according to the USP for weight uniformity test.<sup>18</sup>

Regarding the crushing strength of tablet products, it was determined using tablet hardness tester (Monsanto, Cambridge, UK). For this purpose, ten tablets were randomly selected from each product and force of crushing was recorded. Moreover, friability test was used to assess the resistance of tablet products to any stress that may cause powder loss >1% of the initial weight. Exactly, 20 tablets were taken and weighed from each brand. The selected tablets were subjected to abrasion by using a Roche friabilator (ERWEKA GmbH, Heusenstamm, Germany) at 100 revolutions in 4 minutes (25 revolutions/min). At the end of this procedure, the loss of powder was calculated using the following equation:

$$F(\%) = \frac{W_{\text{initial}} - W_{\text{final}}}{W_{\text{initial}}} \times 100 \quad (1)$$

where  $F$  is the friability,  $W_{\text{initial}}$  is the initial weight, and  $W_{\text{final}}$  is the final weight.

Concerning the disintegration test,<sup>19</sup> six tablets from each product were tested in a freshly prepared medium that contained 0.1 N HCl at 37°C by using ERWEKA disintegration apparatus (ERWEKA GmbH). The disintegration time was the time when no particle remained in the basket of the system. The disintegration time for all products was <10 minutes (accepted limit <15 minutes).

Regarding the release profile of VL from tablet products, 12 tablets of each VL product (alone or in combination) were selected for the dissolution profile tests. The dissolution profile test was carried out using USP Apparatus 2 (paddle) using the recommended US Food and Drug Administration dissolution media. Details of dissolution profile procedure and time intervals of sampling for each product are reported in the related dissolution profile procedure as per the USP 38 and US Food and Drug Administration.

Sample aliquots (10 mL) were withdrawn and replaced with an equal volume of fresh medium to maintain a constant total volume. The samples were filtered through an EMD Millipore filter 0.45 µm. The amount of VL in the samples was determined using the validated HPLC analytical method referenced in Table 1.

The dissolution profile of VL tablet (alone or in combination) was generated from the graph of the percent of VL released versus time using Microsoft Office Excel. The amount of VL in each sample was plotted against time, and similarity ( $f_1$ ) and dissimilarity factors ( $f_2$ ) were calculated according to Equations 2 and 3. The  $f_2$  factor measures the closeness between two profiles, and  $f_1$  measures the difference between two profiles:

$$f_1 = \left\{ \frac{\left[ \sum_{t=1}^n |R_t - T_t| \right]}{\left[ \sum_{t=1}^n R_t \right]} \right\} \times 100 \quad (2)$$

$$f_2 = 50 \cdot \log \left\{ \left[ 1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\} \quad (3)$$

where  $R_t$  and  $T_t$  are the percentages of drug dissolved at each time point for the reference and test products, respectively.

**Table 2** Summary of QC tests of VL tablet products (alone or in combination)

Test	Trade name						Reference of analytical method
	Diovan®	Valzan®	Co-diovan®	Valzan-HCT®	Exforge®	Valzadepin®	
Assay	99.5%	100.0%	100.2%	99.3%	99.7%	98.0%	USP 38
Dissolution	102.0%	104.4%	102.3%	99.1%	99.1%	102.6%	USP 38 <sup>20</sup>
Average tablet weight	310 mg	408 mg	310 mg	408 mg	343 mg	408 mg	BP 2013
$f_2$	81.9		77.3		59		
$f_1$	6.4		1.9		3		

**Abbreviations:** QC, quality control; VL, valsartan; HCT, hydrochlorothiazide; USP 38, United States Pharmacopoeia 38; BP 2013, British Pharmacopoeia 2013;  $f_1$ , similarity factor;  $f_2$ , dissimilarity factor.

An  $f_1$  value  $>15$  indicates significant dissimilarity, and an  $f_2$  value  $>50$  indicates significant similarity.<sup>20–23</sup>

## Results

### In vitro postmarketing surveillance

The six commercial tablet products containing VL included two monotherapy and four combinations (two with HCT and two with AML; Table 1).

Bioequivalence studies were conducted on all these products by the corresponding manufacturers as a requirement of product registration prior to commercialization of premarketing assessment. All these products passed successfully these bioequivalence studies as a precondition of drug registration protocol of the Palestinian Ministry of Health.

Regarding the in vitro postmarketing study, all VL tablet products (brands and the mostly prescribed generic products) were subjected to several QC analyses, including visual and instrumental analyses. There were no visible signs of defects or abnormalities in the shape and color or any sign of spots in any of the tested product. Accordingly, further in vitro investigations were conducted, such as on weight uniformity. All products were in compliance with the USP weight uniformity test, and no single tablet was out of the range as summarized in Table 2.

Regarding hardness and friability, all products showed sufficient resistance strength and did not lose  $>1\%$  of their powder content in the friability tests (Table 2).

As summarized in Table 2, the assay of VL in the monotherapy tablet products and in combination also was within the USP requirements. In fact, the assay of our analyzed products containing VL as mono therapy or combination was always close to 100%.

Concerning tablet dissolution, all products showed complete release of their VL content within 30 minutes (ranging from 99.1% to 102%) as reported in Table 2.

Moreover, the release profile of VL from the generic tablet products was comparable with the related reference listed drug since it showed  $f_2 >50$  and  $f_1 <15$  (Table 2).

### In vivo postmarketing surveillance

#### Demographic analysis

A total of 103 patients were studied in terms of baseline demographic and clinical characteristics as shown in Table 3. About half of the patients were males (53.4%) with an average age between 60 years and 69 years. Less than half of them were of secondary education level (41.7%). The majority of them were nonsmokers (70.9%) and had no other diseases (56.3%).

All patients were included in the study, and most of them (80.6%) were on combination therapy. Over the period of the

**Table 3** Baseline demographics and clinical characteristics of the study population

Baseline characteristic	n	%
Sex		
Male	55	53.4
Female	45	46.6
Age (years)		
20–29	5	4.85
30–39	2	1.9
40–49	8	7.8
50–59	25	24.3
60–69	35	34.0
70–79	17	16.6
80–89	11	10.7
Education levels		
Noneducated	11	10.7
Primary	20	19.4
Secondary	43	41.7
High education	29	28.2
Residency		
City	51	49.5
Village	46	44.7
Camp	6	5.8
Smoking		
Yes	30	29.1
No	73	70.9
Other diseases		
Yes	45	43.7
No	58	56.3

study, 19.4% of patients received monotherapy, and 80.6% patients received the combination therapy (VL in combination with another antihypertensive drug).

Moreover, VL treatment showed that at baseline, 15.5% and 84.5% of patients were prescribed VL at a dose of 80 mg and 160 mg, respectively, either as monotherapy or as combination therapy.

#### Assessment of the efficacy profile

Regarding the efficacy, it was found that the use of the lower dose of VL (80 mg/tablet) was sufficient to produce reduction in both SBP and DBP. In fact, the means were close to each other, and the  $P$ -value was not significant as reported in Tables 4 and 5, respectively.

Moreover, even the same results were observed when the lower dose in combination therapy was compared to the higher dose.

The efficacy of the use of VL alone was compared with that in combination using the same strengths of VL. It was found that the combination was more effective than the monotherapy, resulting in a reduction in both SBP and DBP (Tables 4 and 5, respectively). After 8 weeks, the number of patients who reached BP  $<140/90$  was 70 (68%).

**Table 4** SBP reduction at end of 4 and 8 weeks

	SBP reduction at end of 4 weeks, median (interquartile range)	P-value	SBP reduction at end of 8 weeks, median (interquartile range)	P-value*
Therapy type		0.066		0.331
Monotherapy	15.5 (8.25–20)		20.5 (10.25–30)	
Combination	20 (10–33)		30 (20–40)	
Dosage		0.827		0.007
80 mg	20 (11.25–30)		31.5 (21.25–42.25)	
160 mg	19 (10–30)		27 (20–40)	

**Note:** \*Statistical significance of differences was calculated using the Mann–Whitney *U*-test.

**Abbreviation:** SBP, systolic blood pressure.

### Assessment of the safety profile

In general, our pilot study showed that VL was well tolerated. In fact, only ~6.06% of patients reported AEs. Most of these AEs were of mild-to-moderate intensity. In general, the most frequently reported AEs included headache (17.5%), dizziness (11.75%), and weakness (11.7%) as clarified in Table 6. No serious AEs or death cases were reported during the study period.

Despite the existence of differences in the rate of incidence of some AEs between the two investigated VL strengths as seen in cough, dyspnea, and rash, these differences were not significant since the related *P*-values were >0.05. These AEs may be shown less in 80 mg of VL than in 160 mg of VL as shown in Table 6. However, there are no significant differences in AEs between the uses of combination therapy or monotherapy of VL except for weakness, where the *P*-value was 0.011 as shown in Table 7.

## Discussion

### In vitro postmarketing surveillance

Our in vitro postmarketing surveillance assessment demonstrated a high overall quality of all prescribed VL products as reported in Table 2.

In fact, all products containing VL drug were close to 100%, and the dissolution of the drug was within the recommended international guideline. This indicates that

these products have suitable clinical and safety profiles, and any results in the terms of efficacy and safety should be closely related to patients' factors and not to any defect in the manufacturing of the used product.

### In vivo postmarketing surveillance

Several postmarketing studies were conducted on VL alone or in combination worldwide, in order to investigate the efficacy and safety of these products.<sup>10,11,24</sup>

However, similar studies on Palestinian or Arab patients are not available. Our pilot study showed that a reduction in BP at weeks 4 and 8 was observed similar to other previous studies. However, our studies showed no difference in the reduction between 80 mg and 160 mg strengths in VL alone or in combination. This result was unexpected when compared with other studies where 160 mg dose showed greater BP reduction.<sup>11</sup> Regarding the effect of combination on BP reduction, our results were comparable with similar studies. In fact, the combination showed better BP reduction than VL alone.

Many postmarketing studies were conducted in order to investigate the safety and efficacy of ARBs.<sup>7–9</sup> These studies proved that VL either alone or in combination is well tolerated. However, a Taiwanese study showed that the most frequent AEs were dizziness, headache, and constipation,<sup>11</sup> while a study conducted in England showed that the most frequent AEs were malaise, dizziness, and headache.<sup>10</sup> Moreover,

**Table 5** DBP reduction at end of 4 and 8 weeks

	DBP reduction at end of 4 weeks, median (IQR)	P-value	DBP reduction at end of 8 weeks, median (IQR)	P-value
Therapy type		0.008		0.017
Monotherapy	6.5 (0–10)		9 (4.25–11.75)	
Combination	10 (5–20)		15 (7–22)	
Dosage		0.188		0.721
80 mg	11 (7.75–22.25)		11 (5–32)	
160 mg	10 (4–15)		11 (6–20)	

**Note:** Statistical significance of differences was calculated using the Mann–Whitney *U*-test.

**Abbreviation:** DBP, diastolic blood pressure.

**Table 6** Incidence of adverse effects of VL at two strengths (80 mg and 160 mg/tablet)

Adverse effect	Total, n=103 (%)	VL 80 mg, n=16 (%)	VL 160 mg, n=87 (%)	P-value
Headache	18 (17.5)	3 (18.8)	15 (17.2)	>0.99
Dizziness	12 (11.7)	2 (12.5)	10 (11.5)	>0.99
Diarrhea	2 (1.9)	0 (0)	2 (2.3)	>0.99
Rash	4 (3.9)	2 (12.5)	2 (2.3)	0.113
Nausea/vomiting	4 (3.9)	0 (0)	4 (4.6)	>0.99
Sweating	4 (3.9)	0 (0)	4 (4.6)	>0.99
Arrhythmia	8 (7.8)	2 (12.5)	6 (6.9)	0.607
Weakness	2 (11.7)	1 (6.2)	11 (12.6)	0.686
Cough	2 (1.9)	1 (6.2)	1 (1.1)	0.288
Malaise	4 (3.9)	0 (0)	4 (4.6)	>0.99
Dyspnea	7 (6.8)	2 (12.5)	5 (5.7)	0.297
Indigestion	8 (7.8)	2 (12.5)	6 (6.9)	0.297
Epistaxis	0 (0)	0 (0)	0 (0)	>0.99

**Note:** Statistical significance of differences was calculated using the Fisher's exact test.

**Abbreviation:** VL, valsartan.

dizziness, headache, and upper respiratory tract infection were the most frequently occurring AEs according to a Chinese postmarketing study.<sup>24</sup>

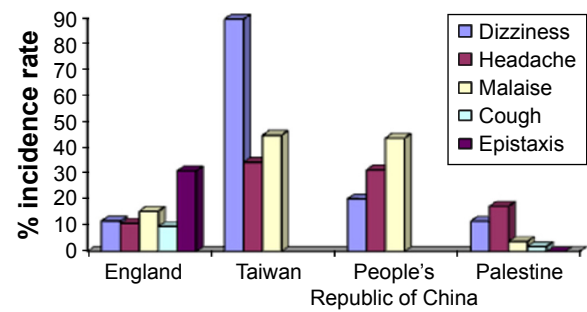
Mainly, the AEs that were obtained in our study were less than the AEs that occurred in other studies as seen in Figure 1. The most frequent AE was headache, which was close to the study conducted in the UK that also showed epistaxis, a rare AE that was not observed in our patients or in Chinese and Taiwanese patients as shown in Figure 1.

**Table 7** Distribution of patients who faced adverse effects from VL alone or in combination

Adverse effect	Total, n=103 (%)	Monotherapy, n=20 (%)	Combination therapy, n=83 (%)	P-value
Headache	18 (17.5)	2 (10)	16 (19.3)	0.514
Dizziness	12 (11.7)	2 (10)	10 (12)	>0.99
Diarrhea	2 (1.9)	0 (0)	2 (2.4)	>0.99
Rash	4 (3.9)	1 (5)	3 (3.6)	>0.99
Nausea/vomiting	4 (3.9)	1 (5)	3 (3.6)	>0.99
Sweating	4 (3.9)	0 (0)	4 (4.8)	>0.99
Arrhythmia	8 (7.8)	1 (5)	7 (8.4)	>0.99
Weakness	12 (11.7)	6 (30)	6 (7.2)	0.011
Cough	2 (1.9)	0 (0)	2 (2.4)	>0.99
Malaise	4 (3.9)	0 (0)	4 (4.8)	>0.99
Dyspnea	7 (6.8)	2 (10)	5 (6)	0.619
Indigestion	8 (7.8)	2 (10)	6 (7.2)	0.651
Epistaxis	0 (0)	0 (0)	0 (0)	>0.99

**Note:** Statistical significance of differences was calculated using the Fisher's exact test.

**Abbreviation:** VL, valsartan.

**Figure 1** The Incidence rates of major AEs of VL in England, Taiwan, People's Republic of China, and Palestine.

**Abbreviations:** AEs, adverse effects; VL, valsartan.

We assessed the efficacy and safety of VL as monotherapy and combination therapy in the Palestinian population. The incidence rates of AEs with VL 160 mg were higher than with VL 80 mg. The most frequently occurring AE was headache. There was no difference in the occurrence of AEs in patients receiving monotherapy or combination therapy.

BP reduction was greater at week 8 than week 4. In addition, the mean SBP reduction at week 8 was significantly greater in patients receiving combination therapy than in those receiving monotherapy. There was no significant difference in the occurrence of AEs between the use of monotherapy and combination therapy, and this proved that the main cause of AEs was VL drug rather than the combined drug, such as HCT or AML.

The main AE in this study was headache (17.5%), which was different from the main AE in the Taiwanese study that was dizziness,<sup>11</sup> and this may be attributed to many reasons. The first reason was using of pilot study with small number of participants that could give different results. Also, VL is known to be one of the medications that is genetic dependent,<sup>7</sup> and there is a race difference between the Palestinian and Taiwanese patients. Moreover, a study that focused on the bioavailability found that it may be different from one country to another.<sup>25</sup> Our study showed that despite the existence of differences in the incidence of certain AEs, these differences are not significant since the *P*-value is >0.05 as seen in cough, dyspnea, indigestion, and rash (Table 6). In a Taiwanese study, the safety profile was independent of dose.<sup>11</sup> Moreover, there is no significant difference in AEs between the uses of combination therapy or monotherapy of VL as clarified in Table 7.

## Conclusion

The in vitro postmarketing surveillance revealed high quality of the used VL tablet products, and accordingly, any result in efficacy or safety should be related to patient's factors and not product defect or substandard quality. The in vivo pilot

postmarketing surveillance conducted on our Palestinian patients showed interesting efficacy profile, since there was no significant difference in BP reduction between both doses (80 mg or 160 mg, alone or in combination). However, a higher reduction in BP was observed when the combination therapy was used despite the strength of VL in the used tablets. Regarding the safety profile of VL, no serious SEs were observed and most of the minor AEs were lower than those observed in patients from other populations. However, future studies with higher number of patients and a wider geographical area are recommended in order to confirm or deny these interesting clinical observations.

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## Disclosure

The authors report no conflicts of interest in this work.

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