ORIGINAL ARTICLE

Safety and effectiveness of a biosimilar biphasic insulin in the management of diabetes mellitus during routine clinical practice in Asian patients

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ABSTRACT

Introduction: Biosimilar insulins have the potential to increase access to treatment among patients with diabetes mellitus (DM), reduce treatment costs, and expand market competition. There are no published studies evaluating the performance of biosimilar insulins in routine clinical practice in Asia. This study assessed the safety and effectiveness of biphasic isophane insulin injection in Malaysian DM patients.

Materials and Methods: In this open label, single-arm, observational, post marketing study, patients received biphasic isophane insulin injection as per the Prescribing Information; and were assessed for safety (adverse events including hypoglycaemia), effectiveness (glycosylated haemoglobin [HbA1c]; fasting blood sugar, [FBS]; and patient's condition by patient and physician) over a period of 24 weeks.

Results: Adult male and female diabetes patients (N=119; type 2 DM, n=117) with a mean (SD) diabetes duration of 13 years were included. No new safety signals have been identified. Significant reduction in HbA1c was observed at weeks 12 and 24 (mean [SD] - baseline: 9.6% [1.9]; Week 12: 9.0% [1.7] and at Week 24: 9.1% [1.7]; p < 0.001). There were 10 serious and 9 non-serious adverse events reported in the study. Expected mild events included hypoglycaemia and injection site pruritus. However, the majority of the adverse events were non-study drug related events. No deaths were reported during the study.

Discussion: Biphasic isophane insulin injection was well tolerated with no new safety concerns. It was found effective in post- marketing studies conducted in routine clinical settings when administered in DM patients in this study.

KEY WORDS:
Insulin, Post-marketing product surveillance, Diabetes, Biphasic, Type 2 diabetes mellitus, Malaysia

INTRODUCTION

Diabetes mellitus (DM) is increasingly being recognised as a potential cause of morbidity and mortality worldwide and is associated with microvascular and macrovascular complications.[1] Global prevalence of DM has increased to 463 million in the year 2019 and is projected to be 700 million by 2045.[2]

Growing population, urbanisation and other risk factors like obesity and hypertension likely contribute to the rise in the prevalence estimates of DM.[3] As per the International Diabetes Association, the prevalence of DM has increased from 11.6% in 2010 to 16.7% in 2019, affecting 3.6 million people in Malaysia.[2] A higher prevalence of DM was reported among Indians (22.1%) than Malays (14.6%) and Chinese (12%).[4]

Diabetes Control and Complications Trial (DCCT) in type 1 diabetes mellitus (T1DM) patients and the UK Prospective Diabetes Study (UKPDS) in type 2 diabetes mellitus (T2DM) patients have demonstrated the usefulness of adequate glycaemic control (glycosylated haemoglobin (HbA1c)<7%) in reducing micro- and macrovascular complications.[5-7] In comparison to oral antidiabetic drugs (OADs), insulin therapy provides good glycaemic control and lowers vascular severities.[5,8]

As recommended by the American College of Endocrinology and the American Association of Clinical Endocrinologists, insulin therapy is usually initiated in T2DM if optimal glycaemic control is not maintained by the combination therapy or when a patient, whether drug naive or on a treatment regimen, presents with HbA1c level >9% and symptomatic hyperglycemia.[9] However, physiological and economic concerns associated with insulin treatment affect initiation, maintenance and optimisation of insulin therapy.[10,11]

In an attempt to make insulin therapy more acceptable and practical for patients and their physicians alike, simple and more convenient insulin formulations have been developed such as biphasic (pre-mixed) insulin. Biphasic insulin contains mixtures of human neutral protamine Hagedorn (NPH) insulin and soluble human (regular) insulin.[7] The combined action of the components provide adequate basal as well as postprandial insulin coverage, and ensures tight glycaemic control with a single formulation.

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The biphasic isophane insulin (BII) injection manufactured by Biocon Limited contains 30% soluble short acting insulin and 70% intermediate-acting NPH.[12] It contains human insulin of recombinant DNA origin manufactured using the yeast, *Pichia pastoris*.[13] The onset of action of BII injection is within 30 minutes after administration.[12] The 30% soluble insulin achieves maximum peak effect 2 hours after administration and 70% NPH achieves maximum peak effect approximately 6 to 8 hours after administration, with a total duration of action of up to 10-12 hours.[12]

Biosimilar insulins have the potential to increase access to treatment among patients with DM, reduce treatment costs, and expand market competition. The BII injection manufactured by Biocon is the first biosimilar insulin approved in Malaysia on the basis of a clinical program that compared the insulin component against the reference product in pharmacokinetics/ pharmacodynamics and safety studies.

The objective of the present study was to determine the safety and effectiveness of biphasic isophane insulin injection during routine clinical practice in patients with DM in Malaysia.

MATERIALS AND METHODS

Study design, Treatments and Patients

This was an open-label, prospective, single-arm, post marketing observational study conducted at two centres in Malaysia: Hospital Putrajaya and Hospital Pulau Pinang. The study protocol was approved by the Malaysian Medical Review and Ethics Committee and the study was carried out in accordance with the principles of the Declaration of Helsinki, ICH E6 Guidance for Good Clinical Practice and local applicable laws and regulations (Malaysian Guidelines for Good Clinical Practice). All patients provided written informed consent prior to the initiation of this study.

A total of 119 DM patients were enrolled in the study. Adult DM patients (>18 years of age) of either gender, who were considered candidates for biphasic insulin therapy by their physicians were included in the study. Patients with known hypersensitivity to human insulin or participating in any other clinical trial were excluded. As this was an observational study in a routine clinical setting, the patients who were on other forms of insulin therapy at the time of enrolment (98%) were switched to BII at baseline.

Patients enrolled in the study received BII injection (100 IU/ml, manufactured by Biocon Limited) administered subcutaneously with reusable INSUpen. Dose was decided by the investigators based on his/ her discretion and the subject's insulin requirement and in accordance with the drug prescribing information.[14] The total duration of observation was for 24 weeks. The study had 2 scheduled visits, at Week 12 and Week 24, after the enrolment/baseline visit.

Concomitant medications were allowed (or dose adjustments were made) for any pre-existing or co-existing illness, as per the physician's discretion.

Safety and Effectiveness Endpoints

The primary objective of the study was to assess the safety and tolerability of the study drug in DM patients during routine clinical practice. The safety endpoints included adverse events (AE) and serious adverse events (SAE) reported by the patient or observed by the Investigator or by any other means during the course of the study. The AEs were coded using the standard medical terminology dictionary, MedDRA ver 19.0 and the drug-reaction relationship was assessed using WHO CAUSALITY assessment definitions.

The secondary objective of the study was to assess the effectiveness of the study drug in DM patients during routine clinical practice. The effectiveness endpoints included changes in HbA1c, overall assessment of the condition of the patients reported by patient and physician, and fasting blood sugar (FBS) from baseline to Week 24.

Statistical Methods

All patients who received at least one dose of the study drug were included in the safety evaluation. Descriptive statistics was used for the patient demography, baseline characteristics and safety endpoints. All patients who had post baseline value for any one of the effectiveness endpoints were included in the effectiveness analysis. Paired t-test was used to test whether the mean of HbA1c and FBS at Week 12 and Week 24 differed significantly from those at baseline. Count data was used to capture percentage of patients with either 'improved' or 'unchanged' condition as per overall assessment by patient and physician. The Z-test for equality of proportions was used to test whether the difference in estimated proportion of an opinion category between physicians and subjects at a specific time point was statistically significant. The level of significance was set at 5% for all statistical tests.

RESULTS

Patient Disposition

Out of the 119 DM patients enrolled, 14 patients (11.8%) dropped out of the study: one patient due to non-compliance, one due to adverse event (seizure) and 12 patients due to unwillingness to continue in the study. One hundred and five patients (88.24%) completed the study. The safety subjects included 119 patients while the effectiveness subjects consisted of 105 patients.

Demographic and Baseline Characteristics

Demography and baseline characteristics of patients are presented in Table I. One hundred and two patients (98%) were already on other forms of insulin therapy prior to entering the study and were then switched to the study drug at baseline.

Metformin was the most common concomitant medication (75%) and the oral anti-diabetic drug (OAD) used by majority of the patients. Other common OADs were vildagliptin-metformin combination (3.81%), glibenclamide (1.90%) and gliclazide (2.86%). A large percentage of patients were also on simvastatin (55%), aspirin (36%), perindopril (34%) and atorvastatin (31%).

Table I: Demographics and baseline characteristics

Demographics and Other Baseline Characteristics	Insugen 30/70 (N=105)
Age (years), mean (SD)	52.4 (11.1)
Weight (kg), mean (SD)	79.4 (16.9)
Height (cm), mean (SD)	162.1 (8.9)
BMI (kg/m^2)	30.0 (5.3)
Sex	
Male, n (%)	58 (55)
Female, n (%)	47 (45)
Duration of diabetes	
< 2	2 (1.9)
2 – 5	11 (10.5)
> 5	91 (86.8)
Unknown	1 (0.9)
Family history	
No	30 (28.6)
Yes	75 (71.4)
Tobacco use	
Non-smoker	83 (79.0)
Ex-smoker	9 (8.6)
Smoker	13 (12.4)
Alcohol use	
Abstainer	98 (93.3)
Occasional	6 (5.7)
Heavy	1 (0.9)
History of hypersensitivity/ allergy to insulin	
No	103 (99.0)
Yes	2 (1.0)
	Type II* (N=104)
Complications	
Microvascular	
Neuropathy	51 (49.0)
Retinopathy	35 (33.7)
Nephropathy	33 (31.7)
Dermopathy	4 (3.8)
Macrovascular	
Coronary heart disease	21 (20.2)
Stroke	5 (4.8)
Peripheral vascular disease	2 (1.9)
Others	2 (1.9)

*No complications were observed with the single Type I patient.

Safety

There were no serious adverse reactions (SAR) and no unexpected adverse reactions were reported. A total of nineteen adverse events were reported (Table II). Among them, ten (8.4%) were serious AEs and nine (7.6%) were non serious AEs. None of the SAEs were considered related to the study drug by the investigator. Among the 10 SAEs, dengue fever (n=1), hypertensive crisis (n=1) and road traffic accident (n=1) were severe, delirium (n=1) and syncope (n=1) were moderate, cellulitis (n=1) and chest pain (n=1) were mild and, diabetic foot (n=1), hyperglycaemia (n=1), and testis cancer (n=1) were unclassified. Of the 9 non-serious AEs, back pain (n=1) and cellulitis (n=1) were moderate and hypoglycaemia (n=2), injection site pruritus (n=1), cellulitis (n=2), cough (n=1) and influenza like illness (n=1) were of mild intensity. Seven out of 9 non-serious AEs (including cough, back pain, cellulitis and influenza-like illness) were not related to the drug, whereas the remaining 2 AEs including hypoglycaemia and injection site pruritus were found possibly/ certainly related to the study drug. No fatality was reported. No new safety signals have been identified.

Effectiveness

Significant reduction in HbA1c levels from baseline was observed at weeks 12 and 24 ($p<0.001$; Table III).

At Week 12, about 87% (91/105) of the patients indicated that their condition was unchanged or improved after treatment with the drug. Similarly, in about 84% (88/105) of the patients, the physicians were of the opinion that condition of the patients remained unchanged or improved. At Week 24, about 83% (88/105) of the patients indicated that their condition was unchanged or improved after treatment with the drug. Likewise, in about 79% (84/105) of the patients, the physicians were of the opinion that condition of the patients unchanged or improved. At weeks 12 and 24, patient's and physician's assessments were in close agreement (p=0.99 at each time point) (Table IV).

At Week 12, FBS decreased by 0.8mmol/L relative to baseline (mean [SD] - baseline: 9.0mmol/L [3.7]; Week 12, 8.2 mmol/L [3.4]; p=0.08). At Week 24, FBS reduced by 0.7mmol/L relative to baseline (mean [SD] - 8.4mmol/L [3.6]; p=0.10).

Table II: List of adverse events and serious adverse events

S. No.	AE/SAE	MedDRA SOC	Intensity Preferred Term	Causality	Action	Outcome
1	SAE	Cellulitis	Mild	Unlikely	Symptomatic treatment and biphasic isophane insulin injection stopped†	Recovered
2	SAE	Chest pain	Mild	Unlikely	Symptomatic treatment and biphasic isophane insulin injection stopped†	Recovered
3	SAE	Diabetic foot	Unclassified	Unlikely	Unknown	Recovered
4	SAE	Dengue fever	Severe	Unlikely	Symptomatic treatment and biphasic isophane insulin injection stopped†	Recovered
5	SAE	Hyperglycemia	Unclassified	Unlikely	Symptomatic treatment	Recovered
6	SAE	Testis cancer	Unclassified	Unlikely	Symptomatic treatment	Unknown
7	SAE	Syncope attack	Moderate	Unlikely	None	Recovered
8	SAE	Road traffic accident Pulmonary contusion Humerus fracture Pubic fracture Flail chest Radial nerve injury	Severe	Unlikely	Symptomatic treatment and biphasic isophane insulin injection stopped†	Recovered
9	SAE	Hypertensive crisis	Severe	Unlikely	Symptomatic treatment	Recovered
10	SAE	Delirium	Moderate	Unlikely	Symptomatic treatment and biphasic isophane insulin injection stopped†	Recovered
11	AE	Seizure‡ Hypoglycemia	Mild	Possibly	Symptomatic treatment and biphasic isophane insulin injection stopped†	Recovered
12	AE	Cough Influenza like illness	Mild	Unlikely	Symptomatic treatment	Recovered
13	AE	Mass	Unclassified	Unlikely	Symptomatic treatment	Recovered
14	AE	Injection site pruritus‡ injection site rash	Mild	Certain	None	Recovered
15	AE	Cough	Mild	Unlikely	Symptomatic treatment	Recovered
16	AE	Cellulitis‡	Mild	Unlikely	Symptomatic treatment	Recovered
17	AE	Back pain Musculoskeletal pain	Moderate	Unlikely	Symptomatic treatment	Unknown
18	AE	Cellulitis	Moderate	Unlikely	Symptomatic treatment	Recovered
19	AE	Hypoglycemia‡	Mild	Unlikely	Symptomatic treatment	Recovered

AE, Adverse Event; SAE, Serious Adverse Event

Note:

†Biphasic isophane insulin injection was stopped, and the patients were switched to other brands during the study.

‡Denotes the alternate aetiology of reported events wherever applicable. Please find them below in their order of appearance in the table:

Seizure: The MedDra SOC preferred term was seizure and hypoglycaemia. The causality of the hypoglycaemic episode was expected to be contributed by patient's non-compliance with meal timings (skipping meals). The hypoglycaemic episodes might have contributed to seizure in the patient. The event hypoglycaemia was an expected AE in the study.

Injection site pruritus: The MedDra SOC preferred term was injection site pruritis and injection site rash. This was an expected AE, possibly related to the study drug.

Cellulitis: The MedDra SOC preferred term was cellulitis. The medical history of the patient showed a long standing, uncontrolled diabetes (HbA1c value between 9.9 mmol/L to 11.6 mmol/L). The patient experienced an episode of cellulitis of left lower limb before initiating biphasic isophane insulin injection therapy. The case was assessed as non-serious and was reported as unlikely to be related to the study drug.

Hypoglycaemia: The MedDra SOC preferred term was hypoglycaemia. The AE was possibly due to pre-existing conditions or concomitant medications and was unlikely to be related to the study drug.

Table III: Summary statistics of mean HbA1c at week 12 and week 24

Laboratory evaluations	N	Mean	SD	Median	Range (min-max)
HbA1c (%) Baseline*	104	9.6	1.9	9.5	(5.9–13.7)
Week 12*	104	9.0	1.7	9.0	(5.8–13.4)
Week 24*	104	9.1	1.7	8.9	(5.5–13.8)

HbA1c, Glycosylated Hemoglobin; *p value≤ 0.001

Paired t-test was used to test whether the mean of HbA1c at Week 12 and Week 24 differed significantly from those at baseline.

Table IV: Overall assessment of biphasic isophane insulin injection treatment by patient and physician at Week 12 and Week 24

S. No.	Assessment	Improved/Unchanged**				Worsened**				Total	
		n		%		n		%		N	
		Pt	Ph	Pt	Ph	Pt	Ph	Pt	Ph	Pt	Ph
1.	Week 12	91	88	86.7	83.8	14	17	13.3	16.2	105	105
2.	Week 24	88	84	83.8	80.0	17	21	16.1	20.0	105	105

Pt, Patient; Ph, Physician; **Z test, p-value >0.05

DISCUSSION

This is the first observational post-marketing study on the safety and effectiveness of BII injection in T2DM patients in routine clinical practice in Malaysia.

Several cross-sectional multicentre studies (DiabCare-Asia study [1998, 2002, 2008]) have revealed that glycaemic levels are poorly controlled across Asia. More than 55% of the population was reported to have HbA1c values exceeding 8%.[14-16] According to the International Diabetes Federation, trends indicate a rapid increase in the prevalence of DM in Malaysia, with a comparative prevalence of 16.7% (2017) in the Western Pacific region.[17] According to a cohort patient registry data from 'Audit of diabetes control and management (ADCM)', there are huge variations in glycaemic control in Malaysia.[18] In 2008, only 22% of the population under treatment were able to achieve the HbA1c target of <7%, the lowest proportion since 1998.[19] Out of the 657,839 patients registered with National Diabetes registry (NDR, 2009-2012), 653,326 patients were diagnosed with T2DM.[20] The T2DM patients audited in 2012 showed a mean HbA1c level of 8.1%, of which only 23.8% of patients were shown to have achieved the glycaemic target (Malaysian glycaemic target) of HbA1c <6.5% in 2012.[21] Given these alarming trends, the use of more intense anti-diabetic therapy should be carefully considered, including the use of injectable recombinant insulin preparations such as BII.

Usage of injectable medications, particularly insulin and glucagon-like peptide-1 receptor analogues (GLP-1 RA) have been on the rise, reflected in Malaysian DiabCare studies after 2003[22,23] and in NDR survey data (usage of insulin increased significantly from 11.7% to 21.4% from 2009 to 2012).[20] DiabCare studies implemented increased the use of insulin (patients on injectable insulin: 2003 - 28%; 2008 - 54% and 2013 - 65%) and this intensified insulin therapy appeared to result in improved DM management in Malaysia.[23]

The first Asian basal insulin evaluation study (FINE) evaluated the effect of basal insulin regimens (NPH, glargine and detemir) in Asian patients with inadequate glycemic control. Data from cohorts from India, China and other Asian countries showed significant ($p<0.001$) reduction in HbA1c (<7%) and fasting plasma glucose levels (<110mg/dL) respectively, with variable occurrence of hypoglycemic episodes (7.1% in India and 27.3% in China).[24]

The BII injection from Biocon Limited, is the first biphasic human insulin formulation (rDNA origin) in the world manufactured using the yeast *Pichia pastoris*. The Pichia expression system is one of the well-developed and unique systems that results in easy scale up of functional proteins and offers combined advantages of *Escherichia coli* and eukaryotic expression systems.[13] The current observational study was conducted to evaluate the safety and effectiveness of BII injection under routine clinical practice in Malaysia. The study recruited 119 DM patients who were candidates for biphasic insulin treatment as per physician's assessment. Though the enrolled patient population consisted of both T2DM (n=117) and T1DM (n=2) patients, the contribution of T1DM patients to the results of the study is small, since the number of T1DM patients was negligible.

No fatality was reported during the study. No SARs or unexpected adverse reactions were reported. Of the nineteen patients (16%) reporting AEs, nine patients (7.6%) experienced non-serious AEs and ten patients (8.4%) had SAEs. No new safety signals were identified at any point during the study. These observations were similar to those reported in other treat to-target studies in DM management.[11]

The occurrence of unfavourable physiological responses such as hypoglycaemia, weight gain or cutaneous reactions (at the injection site) with exogenous insulin poses potential barriers to insulin therapy.[25] Randomised controlled trials on biphasic human insulin, basal detemir, bolus aspart (BB) and biphasic insulin aspart report major episodes of hypoglycaemia and weight gain in T2DM patients.[26] In our study, only two hypoglycaemic episodes and one injection site reaction was reported. The low incidence of hypoglycaemic episodes is of particular importance, considering the significant reductions in HbA1C levels at weeks 12 and 24.

The BII injection produced a significant reduction in the mean HbA1c level at Week 24 ($p\leq0.001$). Reductions were already apparent and statistically significant at Week 12 ($p\leq0.001$), suggesting an early and consistent time-action profile of BII injection within 12-24 weeks (Table III). Considering that the majority of our patients had a long history of diabetes (>5 years; mean duration 13±7 years) which could have led to the development of some degree of insulin resistance; and that it is difficult to employ stringent control on patient compliance in a post-marketing setting, a statistically significant reduction of HbA1c by 0.5% from baseline is considered to be clinically relevant. Elevated level of HbA1c has been identified as a significant risk factor for cardiovascular diseases and stroke in subjects who may have diabetes.[27] Even an increase of 1% in HbA1c concentration was associated with about 30% increase in all-cause mortality and 40% increase in cardiovascular or ischemic heart disease mortality, among individuals with diabetes. Whereas reducing the HbA1c level by 0.2% could lower the mortality by 10%.[28] Hence, statistically significant reduction of HbA1c by 0.5% from baseline is considered to be clinically relevant.

After switching to the study drug, most patients experienced an improved or unchanged disease condition, by both physician's and patient's assessments. Patient's and physician's assessments were in good agreement and did not differ significantly at both Week 12 and Week 24 (Z test p-values >0.05; Table IV). Since most of the patients (98%) enrolled in the study were already on other forms of insulin and were switched to BII injection at baseline, a post-baseline response of either improved or unchanged indicates the effectiveness of the study drug.

FBS levels also showed reductions from the baseline data at Week 12 and Week 24 (reductions of 0.8 mmol/L and 0.7 mmol/L, respectively), though the changes were not statistically significant. The lack of statistically significant reductions may also reflect challenges in compliance to fasting requirements. It should be kept in mind that FBS levels are not the best parameter for assessing long-term glycaemic control, particularly in a post-marketing study; as FBS is likely to be affected by events immediately prior to blood sampling. Finally, the collection and analysis of FBS was done from the perspective of routine monitoring, rather than to demonstrate effectiveness. Reductions in HbA1c and interpretation of disease condition by patients and physicians, summarised above, are more accurate reflections of effectiveness.

It is important to acknowledge the limitations of this study. The number of patients for a post marketing study was relatively small, and it was an open label design, change in disease condition not captured separately as 'improved' and 'unchanged' and challenges in ensuring patient compliance posed by any post marketing study. Our patients were recruited from two hospitals (to study the effectiveness of intervention in routine clinical setting) and thus may lead to selection bias. Despite these limitations, the study reflected real-life clinical use; and hence the results accurately reflect safety and effectiveness of BII injection used in routine clinical practice. Based on the overall assessments, other risk benefit ratio remains favourable for the use of BII injection in the management of DM.

In conclusion, BII injection was well-tolerated, without any safety concerns or new safety signals. It also demonstrated effectiveness by significant reductions in HbA1c and a favourable opinion on overall treatment outcome as reported by patients and the treating physicians.

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DISCLOSURE

Dhanaraj E (corresponding author), Ballari Brahmachari and Mudgal Kothekar are/were employees of Biocon Research Limited.

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