

# The Biosulin equivalence in standard therapy (BEST) study – a multicentre, open-label, non-randomised, interventional, observational study in subjects using Biosulin 30/70 for the treatment of insulin-dependent type 1 and type 2 diabetes mellitus

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**Introduction.** The need for more cost-effective insulin therapy is critical in reducing the burden on patients and health systems. Biosimilar insulins have the potential to dramatically lower healthcare costs by delivering insulin with a similar anti-glycaemic effect and adverse reaction profile.

**Objectives.** The purpose of this study was to confirm equivalence in glycaemic outcomes and side-effect profiles between Biosulin 30/70 and other human premixed insulin preparations on the South African market in a clinical practice setting.

**Methods.** Subjects in this interventional, observational, multicentre, open-label, prospective study were switched from their existing human premix insulin (Actraphane, Humulin 30/70 or Insuman) to the study insulin Biosulin 30/70. The primary endpoint was the change in HbA1c from baseline to 6 months.

**Results.** Seventy-seven adult patients with type 1 ( $n=18$ ) or type 2 ( $n=59$ ) diabetes were enrolled. The baseline HbA1c in the overall cohort was 7.9%, 8.0% at 3 months ( $p=0.50$ ) and 7.6% at 6 months ( $p=0.14$ ). There was a small increase in the total daily dose of insulin used in both the type 1 and type 2 cohort, from 0.62 to 0.65 units/kg/day ( $p=0.0004$ ). There was no significant difference in weight in the study subjects during the 6-month period on Biosulin 30/70 ( $p=0.67$ ).

**Conclusion.** Biosulin 30/70 achieved at least equivalent glycaemic control to existing human premix insulins, with no reported new or severe adverse events. Increased use of biosimilar insulins has the potential for significant cost savings.

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Diabetes accounted for at least \$US465 billion worth of health expenditure in 2011, 11% of the total healthcare expenditure in the 20 - 79-year-old age range.<sup>[1]</sup> According to the International Diabetes Federation (IDF), there are 1.9 million adults with diabetes in this age range in South Africa.<sup>[1]</sup>

The benefits of lifestyle change, exercise and weight loss are definite but difficult to achieve and maintain. Oral medications such as insulin sensitisers and insulin secretagogues are first- and second-line agents in the type 2 diabetes treatment armamentarium and are relatively inexpensive. Newer, more expensive agents (the DPP-IV inhibitors and GLP-1 analogues) have been added to the South African type 2 diabetes treatment algorithm and, although expensive, may further delay the introduction of insulin.<sup>[2]</sup>

Ultimately, however, progressive beta cell failure in patients with type 2 diabetes mellitus results in an ever-increasing proportion of patients requiring injected insulin to obtain and maintain glycaemic targets. Insulin remains the most effective glucose-lowering therapy.<sup>[2]</sup> The addition of insulin dramatically increases the cost of management, with greater requirements for trained diabetes personnel, blood glucose test strips, injection devices, monitoring and the insulin itself.

Biosimilar insulins have the potential to dramatically lower healthcare costs by delivering insulin with similar anti-glycaemic effect and adverse reaction profile to standard, more expensive insulin preparations.<sup>[3]</sup> The purpose of this study is to confirm equivalence in glycaemic outcomes and side-effect profiles between Biosulin 30/70 and other human premixed insulin preparations on the South African market in a clinical practice setting.

## Methods

Seventy-seven subjects with type 1 ( $n=18$ ) and type 2 diabetes mellitus ( $n=59$ ) were enrolled in this interventional, observational, multicentre, open-label, prospective study.

Ethics approval was obtained from the Human Research Ethics Committee of the University of the Witwatersrand. Study subjects were recruited from the Hillbrow Community Hospital Diabetes Clinic (a state hospital facility) and two Centre for Diabetes and Endocrinology (CDE) centres in Johannesburg (private medical facilities). A real-world practice setting was used to gather data on the performance of the insulins across a range of economic and social strata in subjects with type 1 and type 2 diabetes.

Subjects who agreed to participate in the trial and after signing informed consent were enrolled and had anthropometrics measured.

The subjects were then switched from their existing human premix insulin (Actraphane, Humulin 30/70 or Insuman) to the study insulin Biosulin 30/70 after education and demonstration on the new delivery device (the biopen). Most subjects were familiar with pen injection devices. Insulin dosages were kept unchanged at the first visit, but adjusted by the managing physician at subsequent 3-month visit according to their usual practice. No titration algorithm was in force. All oral hypoglycaemic agents and adjuvant medications were continued unchanged.

Blood was drawn at baseline, 3 months and 6 months for measurement of HbA1c. All samples were tested at the National Health Laboratory Services (NHLS) by a turbidimetric inhibition immunoassay (Cobas Integra 400) with a detection limit of 0.1 g/dl. The intra- and inter-assay coefficients of variation were 0.8% and 1.1% respectively. The change in HbA1c from baseline to 6 months was considered the primary endpoint of the study. All adverse events, and in particular the incidence and severity of any hypoglycaemic events, were recorded.

## Results

Seventy-seven adult patients with type 1 ( $n=18$ ) or type 2 ( $n=59$ ) diabetes were enrolled at the 3 study centres. Thirty-six (47%) of the 77 subjects were male. The type 1 cohort had a mean duration of diabetes of 7.2 years (range 1 - 21 years) and the type 2 cohort had been requiring insulin for a mean of 7.4 years (range 1 - 21 years). Patient characteristics are in Table 1. Subjects were grouped according to type of diabetes for better separation of subject characteristics but were pooled for the HbA1c data.

The baseline HbA1c in the overall cohort was 7.9%, 8.0% at 3 months ( $p=0.50$ ) and 7.6% at 6 months ( $p=0.14$ ). The type 1 cohort baseline HbA1c was 8.4% and improved to 8.0% at 6 months ( $p=0.41$ ). The type 2 cohort baseline HbA1c was 7.7%, improving to 7.4% at 6 months ( $p=0.19$ ). There was no statistical difference in the primary endpoint of HbA1c after 6 months in the combined cohort or in the type 1 or type 2 cohorts on Biosulin 30/70 ( $p=0.14$ ) (Fig. 1).

There was a small but significant increase in the total daily dose of insulin used in both the type 1 and type 2 cohorts, from 0.62 to 0.65 u/kg/day ( $p=0.0004$ ). There was no significant difference in weight in the study subjects during the 6-month period on Biosulin 30/70. The mean weight at baseline for the type 1 cohort was 68.1 kg, increasing to 68.6 kg at study end ( $p=0.52$ ), and 91.2 kg declining to 90.8 kg ( $p=0.42$ ) in the type 2 cohort. As expected, their BMIs were essentially unchanged ( $p=0.74$ ).

There were no severe hypoglycaemic episodes reported by the subjects in the 1 month prior to the study (on their pre-study

insulin) and for the duration of the study on Biosulin 30/70. Most of the subjects were managed at the state hospital facility and did not perform self-monitored home blood glucose measurements.

## Discussion

With the humanitarian and economic burdens of diabetes increasing, and with the greatest demands and increases in developing countries, the need for more cost-effective insulin therapy is critical in reducing the financial burden on patients and health systems.

Biosimilars are distinctly different from generic drugs. Generic drugs are chemical entities that have an identical chemical composition to the parent drug and are relatively easy to manufacture. Typically, the delivered cost of a generic product is 10% to 70% that of the 'parent' drug.

Biosimilars, on the other hand, are protein compounds that rely on post-translational modification and folding for efficacy, and therefore are bio-equivalent rather than bio-identical. Because they are foreign proteins, and can elicit an antibody response that can attenuate their function or cause unwanted side-effects, biosimilars must follow precise manufacturing, processing and purification procedures, and are regulated to pass stringent laboratory and clinical trials before approval. Such biopharmaceuticals are made by only a handful of manufacturers using similar techniques involved in producing the parent product, and are therefore termed biosimilar. With many of the insulins reaching the end of their patents, these medications become attractive targets for production of biosimilar insulins. One of the obstacles to the adoption of biosimilar insulin is the notion that

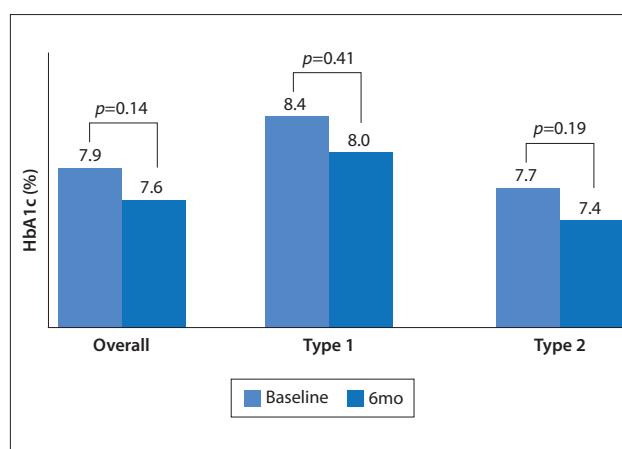


Fig. 1. HbA1c at baseline and after 6 months of therapy with Biosulin 30/70.

Table 1. Patient characteristics and data comparison

	Total			Type 1			Type 2		
	Baseline	6 months	p-value	Baseline	6 months	p-value	Baseline	6 months	p-value
N	77			18			59		
Sex (male/female)	36/41			7/11			29/30		
Age (years), mean (range)	49.7 (26 - 75)			38.9 (26 - 60)			52.1 (26 - 75)		
Duration of insulin use (years), mean	7.3			7.2			7.4		
TDD (u/kg/day) mean±SD	0.62±0.19	0.65±0.20	0.0004	0.71±0.19	0.76±0.18	0.02	0.59±0.19	0.61±0.17	0.01
Weight (kg), mean±SD	85.3±17.2	85.1±16.9	0.67	68.1±9.6	68.6±9.5	0.52	91.2±15.2	90.8±15.1	0.42
BMI (kg/m <sup>2</sup> ), mean±SD	31.1±6.0	31.1±5.9	0.74	25.9±4.1	26.1±4.0	0.55	32.9±5.5	32.8±5.5	0.48
HbA1c (%), mean ± SD	7.9±1.6	7.6±1.7	0.14	8.4±1.6	8.0±1.8	0.41	7.7±1.5	7.4±1.7	0.19

it may be less effective. Some of the concerns have been legitimate, with a number of biosimilar insulins failing to meet stringent registration standards.<sup>[4]</sup> However, ongoing vigilance and extensive clinical trials will continue to be required to ensure the safety and efficacy of new biosimilar insulins.

Biosulin 30/70 L, N and R were approved for use in South Africa by the Medicines Control Council (MCC) in 2005. To achieve this, Biosulin trials by Pharmovs in South Africa demonstrated to the MCC that Biosulin has the same clinical properties as the parent insulin already on the market, and additionally that it did not have any unexpected and new adverse effects in diabetics.

In this non-randomised, interventional 6-month study comparing glycaemic control of existing human insulin mixes (Actraphane, Humulin 30/70 and Insuman) with Biosulin 30/70, Biosulin 30/70 achieved at least equivalent glycaemic control with no reported new or severe adverse events. This surveillance study of Biosulin 30/70 in a real-world medical practice setting expands the safety and efficacy data on record.

Despite the more complex production process and regulatory requirements for biosimilars, they offer a price reduction of between 35% and 50% of the parent insulin and analogue insulins.<sup>[5]</sup>

A meta-analysis to assess the effects of short-acting analogues in patients with type 2 diabetes failed to find any difference in HbA1c between regular human insulin and short-acting analogues.<sup>[5]</sup> There was, however, a small benefit in favour of short-acting analogue insulins in reducing the frequency of severe hypoglycaemic episodes from a median of 1.4 episodes per 100 patient years to 0.3 episodes.<sup>[5]</sup> Horvath *et al.*<sup>[6]</sup> compared long-acting analogues Detemir and Lantus

with NPH insulin in adult patients with type 2 diabetes and also found no A1c advantage. The efficacy of these analogue insulins in type 1 diabetes is more established although the actual advantages are minimal.<sup>[7]</sup>

Overall, more expensive analogue insulins offer minimal advantages over regular insulin in the management of type 2 diabetes, and increased use of biosimilar insulins has the potential for significant cost savings with no loss in patients' glycaemic outcomes. There is no doubt that biosimilar insulins such as Biosulin will play an ever-increasing role in the management of diabetes.

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