FINAL CLINICAL STUDY REPORT

Product: Insugen® R and Insugen® N

A Randomised, Active Controlled, Parallel Group, Multicentre, Two-Phase, Open-Label Study Comparing the Safety and Immunogenicity of Insugen® R and Insugen® N with Actrapid and Insulatard in Patients with Type 1 Diabetes Mellitus

Protocol Number: INSUGCT300509

Study Initiation Date (first patient enrolled): 04 October 2010
Study (Phase 2) Completion Date (last patient completed): 14 July 2012

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The trial described in this report was performed according to the ethical principles described in the Declaration of Helsinki (1964), the International Conference on Harmonisation Good Clinical Practice (ICH GCP) E6, and Schedule Y of the Drugs and Cosmetics Act and Rules (as amended 2005) issued by the Government of India. This clinical study report was prepared according to the ICH Harmonised Tripartite Guideline E3: Structure and Content of Clinical Study Reports, 30 Nov 1995.

2. SYNOPSIS

NAME OF SPONSOR/COMPANY: Biocon S.A., Switzerland NAME OF FINISHED PRODUCT: Insugen® R and Insugen® N NAME OF ACTIVE INGREDIENT(S): insulin and isophane insulin	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol No.: INSUGCT300509 (version 3.0, 08 November 2011)

This clinical study report is the final report on the 48-week study. Results from phase 1 of the study are also presented.

Title of Study: A randomised, active controlled, parallel group, multicentre, two-phase, open-label study comparing the safety and immunogenicity of Insugen R and Insugen N with Actrapid and Insulatard in patients with type 1 diabetes mellitus

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Publication (Reference): None.

NAME OF SPONSOR/COMPANY: Biocon S.A., Switzerland NAME OF FINISHED PRODUCT: Insugen® R and Insugen® N NAME OF ACTIVE INGREDIENT(S): insulin and isophane insulin	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Study Period (First Patient, First Visit/Last Patient, Last Visit of Phase 2): 04 October 2010 to 14 July 2012		**Phase of development:** 3

Objectives:

Primary: To evaluate the safety and immunogenicity of Insugen R plus Insugen N compared to European Union (EU)-sourced Actrapid® plus Insulatard® in patients with type 1 diabetes mellitus (T1DM).

Secondary: To evaluate the efficacy of Insugen R plus Insugen N compared to EU-sourced Actrapid plus Insulatard in patients with T1DM.

Methodology: This was a multicentre, 2-phase, open-label study comparing the safety, efficacy, and immunogenicity of Insugen R plus Insugen N versus Actrapid plus Insulatard in patients with T1DM. Phase 1 was a comparative, randomised, parallel assignment phase in T1DM patients receiving 24 weeks of treatment with Insugen R plus Insugen N compared to patients receiving 24 weeks of treatment with Actrapid plus Insulatard. Phase 2 was a noncomparative 24-week extension period in which patients previously on Actrapid plus Insulatard were switched to Insugen R plus Insugen N so that all patients received Insugen R and Insugen N during this phase. The study consisted of the following periods: screening (day -49 to day -29), run-in (day -28 to day -1), baseline/randomisation (day 0), phase 1 treatment (day 1 to day 168), and phase 2 treatment (day 169 to day 336). Patients went through a screening period of 1 to 3 weeks during which they were evaluated for inclusion and exclusion criteria, followed by a 4-week run-in period during which the patients were stabilised on EU-sourced Actrapid and Insulatard. After the run-in period, the patients were randomised and stratified by region (EU, Ukraine, and India), with a ratio of 1:1 to either Insugen R plus Insugen N for 48 weeks (arm A) or EU-sourced Actrapid plus Insulatard for the first 24 weeks, followed by 24 weeks of Insugen R plus Insugen N (arm B).

Number of Patients (planned and analysed): A total of 286 patients (230 in Germany, Hungary, Italy, Romania, Ukraine; and 56 in India) were planned to be enrolled. A total of 294 patients were randomised and analysed for safety in phase 1. Phase 1 and 48-week (phase 1 and phase 2 combined) efficacy analyses were performed using the modified intent-to-treat population, consisting of 294 patients. For phase 1 analyses, the per-protocol (PP) population, consisting of 236 patients, was used for selected endpoints. In phase 2, 276 patients were analysed for safety. Analyses of phase 1 and phase 2 data combined were performed using data from 276 patients.

Diagnosis and Main Criteria for Inclusion: Patients with T1DM with the following inclusion criteria were enrolled into the study:

- Provided written informed consent
- Male and female patients between the ages of 18 to 80 years, inclusive
- Diagnosed with T1DM before 40 years of age and must have been on treatment with insulin for at least 1 year (confirmed by interview with the patient); fasting plasma C-peptide ≤0.2 pmol/mL (≤200 pmol/L or ≤0.6 ng/mL or ≤0.2 nmol/L); and/or a history of initiation of insulin treatment within 6 months after diagnosis (confirmed by interview with patient)
- At least 3 months on basal-bolus insulin therapy before enrolment requiring 3 or more daily injections
- Body mass index of 18.5 to 34.99 kg/m^2, inclusive
- Stable weight with no more than 5-kg gain or loss within 3 months of screening (obtained by patient history)
- Glycosylated haemoglobin (HbA1c) ≤11.0% at screening. One retest was permitted within the screening

timeline, if required

- Ability and willingness to perform blood glucose profiles using blood glucose meter at home during the study

Exclusion Criteria: To participate in the study, none of the following criteria could apply to any patient:

- History of hypersensitivity to any of the active or inactive ingredients of the test and/or reference products
- Clinically significant abnormality (including laboratory values) at screening, on the basis of which the investigator advised against study inclusion
- Electrocardiogram abnormality at screening considered clinically significant by the investigator
- Use of insulin pump therapy in the past 2 months before screening
- Moderate insulin resistance, defined as requiring insulin of ≥1.4 IU/kg/day
- Significant history of atopy or allergic drug reactions
- Clinically significant major organ disease before screening, except for well-controlled and stable conditions such as essential hypertension (blood pressure >130/80 mmHg), well-controlled hyperlipidaemia, and thyroid disorders for at least 3 months before screening
- Knowledge of secondary complications of diabetes:
  - Retinopathy: moderate to severe nonproliferative diabetic retinopathy or proliferative diabetic retinopathy of any severity or history of treatment with laser surgery/vitrectomy within 6 months of the screening visit
  - Nephropathy: proteinuria ≥1+ by urine dipstick in the absence of infection or vaginal contamination and/or serum creatinine ≥1.5 times of upper limit of reference range; one retest was permitted within the screening timeline, if required; history of renal transplant
  - Neuropathy: history or finding of severe form of sensorimotor, cardiac, gastrointestinal, or genitourinary autonomic neuropathy
  - Peripheral vascular disease: severe peripheral vascular disease that had resulted in amputation, chronic foot ulcer, claudication on walking <200 m, or absent pulses
- Unstable coronary artery disease (unstable angina, myocardial infarction within the preceding 6 months), heart failure (New York Heart Association Grade 2 or higher), history of stroke, or transient ischemic attack within the preceding 6 months
- History of drug or alcohol dependence or abuse within 6 months before screening
- Current use of systemic or inhaled glucocorticoids or other drugs that may affect glycaemic control
- Treatment with blood-glucose lowering drugs other than insulin or insulin analogues in the 4 weeks before screening or during the study
- Use of prohibited concomitant medications, including oral hypoglycaemic agents; monoamine oxidase inhibitors; β-blockers; salicylates >300 mg/day or chronic usage requiring uninterrupted administration for >14 days during the study; anabolic steroids; diltiazem; niacin; isoniazid; epinephrine; thiazide diuretics if >25 mg/day; and loop diuretics
- History of 2 or more episodes of hypoglycaemia requiring assistance by another person to administer glucose or glucagon (severe hypoglycaemia) within 6 months before screening
- Any hospitalisation or emergency department visit due to poor diabetes control within 6 months before screening
- Any electively planned surgery requiring hospitalisation
- Pregnancy, breastfeeding, or planned pregnancy during the study duration. Women of childbearing potential (any woman who was not surgically sterile or >2 years postmenopause) must have agreed to use a reliable method of contraception (eg, double-barrier, tubal ligation, or stable hormonal contraception) throughout the study period. Women who became pregnant during the study must be discontinued from

the study and followed for pregnancy outcome

- Impaired hepatic function (alanine transaminase or aspartate aminotransferase value >2 times the upper limit of normal and/or serum bilirubin >1.5 times the upper limit of normal at the screening visit); one retest was permitted within the screening timeline, if required
- Impaired renal function (serum creatinine ≥1.5 times of upper limit of reference range at screening) or chronic kidney disease (estimated glomerular filtration rate <60 mL/min/1.73 m^2)
- Haemoglobinopathies, haemolytic anaemia, anaemia of chronic disease, or any factor affecting the measurement of HbA1c
- Receipt of another investigational drug within 6 weeks before screening or within 5 half-lives of the drug, whichever was longer, or scheduled treatment of another investigational drug during the current study period
- Any patient who in the estimation of the investigator did not show necessary compliance to participate in the study and comply with necessary study requirements

Test Product: Insugen R plus Insugen N

Dose and Mode of Administration: Study medications were self-administered subcutaneously into the thigh or abdominal wall at home on a daily basis in accordance with the needs of the patient. The goal of titration during the run-in period was preprandial capillary glucose between 70 and 130 mg/dL and 2-hour postprandial capillary glucose of <180 mg/dL. After the run-in period, the dose adjustments were to be done to meet the same goals. Patients were advised to call the investigator for insulin dose adjustment if they had any measured capillary glucose value of ≤70 mg/dL (3.9 mmol/L) or if they had symptoms suggestive of hypoglycaemia. In phase 2, the initial dose of Insugen R and Insugen N for patients who were randomised on arm B was the same as that of the reference products.

Batch Nos.: Insugen R: I170032, I170060; Insugen N: I180035, I180067, I180097

Reference Product (Phase 1): EU-sourced Actrapid plus Insulatard

Dose and Mode of Administration: Dose and mode of administration was similar to test product. The initial dose recommendation of Actrapid and Insulatard for patients who were on other types of insulin (other than the reference products) or insulin analogues were decided by the investigator based on his or her experience and/or the respective prescribing information.

Batch Nos.: Actrapid: AS60350, XS63196; Insulatard: YS61186

Duration of Treatment (Comparative Phase and Noncomparative Phase):

Arm A: Insugen R plus Insugen N for 48 weeks

Arm B: EU-sourced Actrapid plus Insulatard for the first 24 weeks, followed by 24 weeks of Insugen R plus Insugen N

Criteria for Evaluation:

This final clinical study report presents safety, efficacy, and immunogenicity data for the phase 1 comparative portion of the study as well as data for the entire 48 weeks of the study.

Immunogenicity: Immunogenicity was evaluated by change in mean anti-insulin antibody binding percentage, change in mean anti-insulin antibody titres, and change in incidence of anti-insulin antibodies. Incidence of anti–host-cell protein (HCP) antibodies and incidence of neutralising antibodies (NAb) were also assessed. A serum sample to assess anti-insulin antibodies and anti-HCP antibodies was obtained at screening, baseline, weeks 4, 8, 16, 24, 32, 40, and 48.

Efficacy: Efficacy was evaluated by change in HbA1c, change in fasting plasma glucose (FPG), change in

average 7-point capillary blood glucose profile (7-PCBG), and change in prandial and basal insulin dose. HbA1c was obtained at screening, baseline, and weeks 8, 12, 20, 24, 36, and 48; FPG was obtained at screening, run-in, baseline, and weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48. Patients completed 7-PCBG at home during the week preceding each study visit during the treatment period. These data, along with the prandial and basal insulin dose, were transcribed from the patient diary to electronic case report form at scheduled visits.

Safety: Safety was evaluated by frequency of injection-site reactions, frequency of systemic allergic reactions, frequency of hypoglycaemic events per 100 patients per month, partial correlation between allergic reactions (local and systemic) and insulin percentage binding antibodies, adverse event (AE) assessments, change in physical examination including body weight, change in vital signs, and laboratory assessments. These were recorded at each visit or as specified by the protocol. Electrocardiograms were conducted at screening and at weeks 24 and 48.

Statistical Methods:

Immunogenicity Analyses

For all immunogenicity assessments, visit 3 values were used as baseline. If the baseline value was missing, screening values were used as baseline. For change in anti-insulin antibody binding percentage, separate analyses were also done where only baseline values were used, and patients with missing values at baseline were not considered. In addition, change in anti-insulin antibody percent binding was analysed for all patients as well as for only those patients who were 'true positives' for anti-insulin antibody.

The primary variable for the study was mean anti-insulin antibody binding percentage. This was used to establish the comparability of Insugen R plus Insugen N with Actrapid plus Insulatard in terms of immunogenicity.

The change in mean anti-insulin antibody binding percentage between baseline and week 24 and week 48 was analysed using an analysis of covariance. Treatment group was a fixed effect, and anti-insulin antibody binding percentage at baseline and region were included as covariates. Comparisons between the treatment groups were estimated using a 2-sided 95% confidence interval (CI) for differences in least squares means (LSMs) at week 24 and week 48. The primary analysis was performed on the modified intent-to-treat population. For phase 1, analysis was also performed on the PP population as a supportive analysis.

The secondary immunogenicity variables were comparison of the change in mean anti-insulin antibody titres and comparison of the change in incidence of anti-insulin antibodies. Incidence of anti-HCP antibodies and incidence of NAb were also assessed but were not secondary variables. For the NAb analysis, if the magnitude of response for a sample was below NAb assay cut point (ACP), the sample was considered positive, and if the magnitude of response for a sample was above NAb ACP, then the sample was considered negative.

Immunogenicity samples were determined to be positive or negative based on the screening ACP and confirmatory ACP (the screening and confirmatory steps were performed together). The confirmatory step was based on percent inhibition of anti-drug antibodies (ADA) binding to labelled drug in the presence of unlabelled drug. If percent inhibition was above the confirmatory cut point, the sample was positive for ADA.

Summary statistics were produced at each visit, including change from baseline at each visit after baseline. For this comparison, 2 types of analysis were performed. For the first analysis, the incidence of patients positive for anti-insulin antibodies at week 24 was compared between treatment groups using chi-square analysis, including only those patients whose results were originally negative for antibodies at baseline. A 2-sided 95% CI was provided. For the second analysis, within-treatment comparisons were explored using a McNemar chi-square approach. For the noncomparative phase, values were tabulated by comparative-phase treatment arm,

and totals were tabulated for the noncomparative phase.

The incidence of anti-HCP antibodies was summarised for baseline and week 24 and week 48 with a frequency table for the number of patients with a positive test and the number of patients with a negative test. For patients randomised to the Insugen R plus Insugen N group, the incidence of anti-HCP antibodies was explored using a chi-square approach.

Efficacy Analyses

The following outcomes were analysed:

- Change in HbA1c from baseline to week 24 and to week 48
- Change in FPG from baseline to week 24 and to week 48
- Change in average 7-PCBG profile from baseline at each visit
- Change in prandial, basal, and total insulin doses (absolute dose as well as dose adjusted by weight) from baseline to week 24 and to week 48
- Change in Diabetes Treatment Satisfaction Questionnaire (DTSQ) status score and DTSQ change score from baseline to week 24
- Partial correlations between change in HbA1c from baseline to week 24 and to week 48 and change in percentage of anti-insulin antibody binding were evaluated, conditioned on changes in prandial and basal insulin doses during the 24-week comparative phase and during the entire 48 weeks.
- Partial correlations between changes in prandial and basal insulin doses and changes in percentage of anti-insulin antibody binding were evaluated, conditioned on changes in HbA1c, during the 24-week comparative phase and during the entire 48 weeks.

Safety Analyses of Particular Interest

Local and systemic tolerability was analysed. For each assessment date, incidences of the symptoms were summarised in terms of frequency of patients globally (at least 1 symptom) and for each symptom. Local and systemic incidence tables (based on investigator assessments in the electronic case report form) were provided.

For hypoglycaemic events, the adjusted (100 patients/month) incidence rates with 95% CI were estimated within each treatment group. In addition, a partial correlation was carried out between allergic reactions with percent antibody binding.

Summary of Results and Overall Conclusions

Immunogenicity Results:

- The analysis of the primary endpoint, comparison of arms A and B for mean change in anti-insulin antibody binding percentage from baseline to week 24, did not reveal any notable difference between Insugen R plus Insugen N and Actrapid plus Insulatard treatments. Considering only patients with positive confirmatory assay results, mean (± standard error) changes at week 48 in anti-insulin antibody binding percentage were 4.10 ± 0.793% for the Bio/Bio arm and 4.88 ± 0.806% for the Ref/Bio arm.
- Changes in anti-insulin antibody titres from baseline to week 24 and to week 48 were comparable in both treatment groups, although high variability in the data was observed. Patients who received Insugen during the comparative phase had a median change from baseline of 9.05%, and patients who received Actrapid plus Insulatard had a median change from baseline of 8.09%.
- The incidence of anti-insulin antibodies at baseline, week 24 and at week 48 was similar between the comparative-phase treatment groups, and the incidence of new positives detected at week 24 and 48 was

also comparable between groups.

- When patients on the comparator treatment in phase 1 of the study switched to Insugen in phase 2 of the study, the changes in anti-insulin antibody binding percentage, anti-insulin antibody titre, incidence of anti-insulin antibodies, as well as anti-HCP antibodies changes, were similar to those who continued on the Insugen arm. Hence it can be concluded that switching from Actrapid plus Insulatard to Insugen R plus Insugen N in the this study did not lead to any clinically meaningful differences in the immunological test results.
- There was no meaningful increase in anti-HCP antibodies over the course of the trial. A proportion of patients (about 30%) were positive for anti-HCP antibodies at baseline in both treatment arms. The incidence of total as well as new anti-HCP antibody positives was comparable at week 24 and 48 in both treatment arms. The incidence of anti-HCP antibodies at week 48 was 8.6% for patients who received Insugen in the comparative phase and 10.3% for patients who received Actrapid plus Insulatard in the comparative phase. The anti-HCP positivity in the comparator arm is likely due to cross-reactivity between the anti-HCP detection method (specific for *Pichia pastoris*) and *Saccharomyces* HCP that may be ubiquitous in many individuals. The presence of anti-HCP antibodies showed no correlation with efficacy or safety, for either the test or the reference arm.
- Using the 1% false-positive ACP, no patients were positive for NAb at baseline, week 24, or week 48 in either treatment arm. Over the course of the trial, 7 patients in arm A/Bio-Bio demonstrated NAb positivity, each at a single visit. These represent 7 out of 909 (0.77%) immunogenicity samples analysed in total from patients treated with Biocon insulin. No safety issues (including hypoglycaemia) were reported for these NAb-positive patients. This transient positivity was not correlated with loss of efficacy, or increase in the daily requirement of the insulin dose in an effort to maintain glycaemic levels.

Efficacy Results:

- Insugen R plus Insugen N was noninferior to Actrapid plus Insulatard with respect to the secondary endpoint change in HbA1c from baseline to week 24. For the primary analysis (PP population), the LSM treatment difference (arm A – arm B) in the change from baseline at week 24 was 0.03% (95% CI, –0.23, 0.29). The upper bound of the 95% CI (0.29%) was less than the noninferiority margin of 0.4%.
- Mean HbA1c values from baseline through week 24 to week 48 showed negligible change in the arm treated with Insugen R and Insugen N throughout. The maximum difference noted was an improvement of 0.29% at week 12 and worsening of 0.11% noted at week 36; with a final difference of 0.06% improvement noted at the end of study. This indicates that the Biocon products, Insugen R and Insugen N sustained efficacy over the long term.
- Change in mean HbA1c value from baseline to week 24 and from week 24 to week 48 was similar between comparative-phase treatment groups. Importantly, over the course of the 48 weeks of the trial, the pattern of changes in HbA1c was similar in both arms, even after the transition from phase 1 to phase 2. The peaks and troughs occurred at the same visits. This indicates that the switch from Actrapid plus Insulatard to Biocon insulins had no effect on efficacy.
- The mean postprandial insulin requirement over the duration of the study was also similar in both treatment arms; in addition, the postprandial glucose control was maintained at target postprandial levels in both arms until 24 weeks, suggesting similarity in efficacy between Insugen R and Actrapid. The mean basal insulin dose was also similar in both arms over phase 1, demonstrating similarity in efficacy between Insugen N and Insulatard.
- The remaining secondary efficacy endpoints FPG levels and 7-PCBG showed no notable difference

between the treatment arms at week 24. The perception of glycaemic control at week 24 was similar between the treatment arms, as indicated by the DTSQ scores recorded during the comparative phase.

- Multiple correlations were done to check for interactions between change in HbA1c, change in anti-insulin antibody (binding percentage and titre), and change in basal and prandial insulin doses. No notable correlation was seen for any of these parameters, for either arm and in either phase of the study.

Safety Results:

In the comparative phase:

- The incidence of AEs of special interest (AESIs) such as injection-site reactions, systemic reactions, and hypoglycaemic events was comparable in both treatment arms.
- Hypoglycaemic events, both symptomatic and asymptomatic (based on glucose values ≤70 mg/dL) were comparable in both treatment arms, with similar risk ratios at week 4 (symptomatic: 1.07) and week 24 (symptomatic: 1.00) in the study, suggesting that switching from Actrapid plus Insulatard to the Insugen R plus Insugen N treatment arm did not increase the risk of hypoglycaemia through 24 weeks of treatment.
- The overall incidence of AEs and serious AEs (SAEs) was similar across both treatment arms, as was the severity of AEs. No patients died.
- In conclusion, the safety profile of the Insugen R plus Insugen N and Actrapid plus Insulatard arms were very similar.

In the noncomparative phase:

- One patient, who later discontinued, experienced mild injection-site irritation during the noncomparative phase. This patient had shifted to Insugen R plus Insugen N from Actrapid plus Insulatard.
- The frequency of total and symptomatic hypoglycaemic events were comparable between the treatment arms until week48 (reflected in the risk ratio, 1.04; 95% CI, 0.93, 1.17). An increase in events occurred in both arms at month 7; this was considered unlikely to be clinically irrelevant, and possibly represented more intensive monitoring rather than an effect of treatment.
- Patients on Insugen R plus Insugen N throughout the study had 53 treatment-emergent AEs (TEAEs) in phase 1 and 29 TEAE in phase 2; as expected, AEs decreased in occurrence with continuing exposure. Patients who were on Actrapid plus Insulatard and shifted to Insugen R plus Insugen N also showed a similar decrease (from 41 TEAEs in phase 1 to 36 in phase 2), which indicates that the switch in treatment was not associated with any change in the incidence of AEs.
- In conclusion, no appreciable difference in safety findings was noted for the noncomparative phase compared to the comparative phase, for either treatment group. Data gathered over the full 48 weeks of exposure demonstrates the safety of Insugen R plus Insugen N. Furthermore, the switch from Actrapid plus Insulatard to Insugen R plus Insugen N was not associated with any change in the incidence of AEs.

Discussion

Immunogenicity:

- The analysis of the primary endpoint, mean change in anti-insulin antibody binding percentage from baseline to week 24, did not reveal any notable difference between Insugen R plus Insugen N and Actrapid plus Insulatard treatments. At week 48, mean (± standard error) change in anti-insulin antibody binding percentage was 4.10 ± 0.793% for the Bio/Bio arm and 4.88 ± 0.806% for the

Ref/Bio arm.

- In both phases of the study, the 2 groups had similar numbers of patients who seroconverted and were identified as new positive cases (ie, who did not have anti-insulin antibodies at baseline but did at week 24/week 48).
- Changes in anti-insulin antibody titres from baseline to week 24 and to week 48 were comparable for both treatment groups (though highly variable).
- The incidence of anti-insulin antibodies at baseline, week 24, and week 48 was similar between treatment groups.
- There was no meaningful increase in anti-HCP antibodies over the course of the trial. Up to 30% of the patients developed anti-HCP antibodies; in both treatment groups. Ten patients who received Actrapid plus Insulatard during the comparative phase seroconverted after week 24; as compared to 5 who received Insugen N and R during the comparative phase. The anti-HCP positivity in the comparator arm is likely due to cross-reactivity between the anti-HCP detection method (specific for *P. pastoris*) and ubiquitously present *Saccharomyces* HCP. The presence of anti-HCP antibodies showed no correlation with efficacy or safety, for either the test or the reference arm.
- Using the 1% false-positive ACP, no patients were positive for NAb at baseline, week 24, or week 48 in either treatment arm. Over the course of the trial, 7 patients in arm A/Bio-Bio demonstrated NAb positivity, each at a single visit. These represent 7 out of 909 (0.77%) immunogenicity samples analysed in total from patients treated with Biocon's insulin. The positivity of NAb was not correlated with an increase in antibody titres. No safety issues (including hypoglycaemia) were reported for these NAb-positive patients. This transient positivity was not correlated with loss of efficacy, or increase in the daily requirement of the insulin dose in an effort to maintain glycaemic levels.
- When patients on the comparator treatment in the phase 1 of the study switched to Insugen in phase 2 of the study, the changes in anti-insulin antibody binding percentage, anti-insulin antibody titre, incidence of anti-insulin antibodies, as well as anti-HCP antibodies changes, were similar to those who continued on the Insugen arm. Hence it can be concluded that switching from Actrapid plus Insulatard to Insugen R plus Insugen N in the trial did not lead to any clinically meaningful differences in the immunological test results.
- Considering the immunogenicity data overall (mean values and change from baseline for antibody binding percentage and antibody titre, rate of new positives and rate of NAb-positives), Insugen R plus Insugen N treatment did not raise any immunogenicity concerns affecting safety or efficacy in patients exposed for the full 12 months.

Efficacy:

- Insugen R plus Insugen N was found to be noninferior to Actrapid plus Insulatard with respect to change in HbA1c from baseline to week 24. The treatment difference was 0.03%, with the upper bound of the 95% CI (–0.23, 0.29) being lower than the noninferiority margin of 0.4%.
- Mean HbA1c values from baseline through week 24 to week 48 showed negligible change in patients treated with Insugen R and Insugen N throughout the study. The maximum difference noted was an improvement of 0.29% at week 12 and worsening of 0.11% noted at week 36; with a final difference of 0.06% improvement noted at the end of study. This indicates that the Biocon products, Insugen R and Insugen N maintained comparable efficacy over the long term.
- Importantly, over the course of the 48 weeks of the trial, the pattern of changes in HbA1c was very similar in both arms, even after the transition from phase 1 to phase 2. The peaks and troughs

occurred at the same visits. This indicates that the switch from Actrapid plus Insulatard to Biocon insulins had no effect on efficacy.

- The mean postprandial insulin requirement over the duration of the study was similar in both arms; in addition, postprandial glucose control was maintained at target postprandial levels in both arms until 24 weeks suggesting similarity in efficacy between Insugen R and Actrapid. The mean basal insulin dose was also similar in both arms over phase 1, demonstrating similarity in efficacy between Insugen N and Insulatard.
- The remaining secondary efficacy endpoints FPG levels and 7-point capillary blood glucose levels showed no notable difference between the treatment arms at week 24. Similar FPG control in both arms suggests similarity in efficacy between Insugen N and Insulatard, considering control of fasting glucose as a function of efficacy of the intermediate-acting insulins.
- The perception of glycaemic control at week 24 was similar between the treatment arms, as indicated by the DTSQ scores recorded during the comparative phase.
- Multiple correlations were done to check for interactions between change in HbA1c, change in anti-insulin antibody (binding percentage and titre) and change in basal- and prandial insulin doses. No notable correlation was seen for any of these parameters, for either arm and in either phase of the study.
- The overall assessment of the above results suggests that Insugen R and Insugen N are individually similar to Actrapid and Insulatard in efficacy.

Safety:

- Over the entire study, one mild injection-site reaction was reported (in the noncomparative phase, in a patient initially randomised to Actrapid plus Insulatard). Two patients (both randomised to Insugen R plus Insugen N) reported systemic allergic reactions; one during the comparative phase and one during the noncomparative phase. The systemic allergic reaction during the noncomparative phase actually did not meet the criteria for an AESI and was reported in error.
- During the comparative phase, hypoglycaemic events (both symptomatic and asymptomatic) were comparable in both treatment arms, with similar risk ratios at week 4 and week 24; suggesting that switching from Actrapid plus Insulatard to the Insugen R plus Insugen N treatment arm did not increase the risk of hypoglycaemia through 24 weeks of treatment. The two arms also had similar numbers of hypoglycaemic events at fasting condition time points and similar incidence of nocturnal hypoglycaemia (attributable predominantly to the intermediate-acting insulins).
- During the noncomparative phase, the frequency of hypoglycaemic events did not increase for either treatment group. The frequency of events generally decreased over the last 5 months of treatment for both treatment arms. The risk ratio at week 48 was 1.04; showing that the two groups had similar rates of hypoglycaemia.
- In the comparative phase, similar proportions of patients in the two arms reported TEAEs. Three patients in each arm reported SAEs; of which 2 (hypoglycaemia and hypoglycaemic seizure) were considered ‘probably’ related to study medication.
- In the noncomparative phase also, similar proportions of patients in the two groups reported TEAEs. Hypoglycaemia was the most common (2.5% of all patients). The majority of TEAEs were mild or moderate in severity. Five patients reported 8 treatment-emergent SAEs. No patients withdrew due to a TEAE.
- In summary, no appreciable difference in safety findings was noted between the 2 treatment groups,

neither during the comparative phase nor during the noncomparative phase. There were no notable differences observed of clinical significance when patients switched from comparator drug to Biocon insulins in phase 2 of the study.

Overall Conclusion:

Over the course of this study, there were no clinically relevant differences between Insugen R plus N and Atrapid plus Insulatard treatments; for antibody binding percentage, antibody titre, incidence of NAb, insulin dose requirement, fasting and prandial glucose level, DTSQs scores for frequency of hypoglycaemia/ hyperglycaemia, change in HbA1c, risk of hypoglycaemia, or rates of TEAEs. Therefore, Insugen R plus N and Actrapid plus Insulatard are similar in immunogenicity, efficacy, and safety.

No appreciable changes in safety, efficacy and immunogenicity were seen in patients switched from Actrapid plus Insulatard to Insugen R plus N in the noncomparative phase.

From data collected over the entire study, Insugen R plus Insugen N was found to be safe and well-tolerated. The immunogenicity results did not correlate with safety issues or changes in efficacy or insulin dose requirement and are therefore considered to have no particular concern in the long-term treatment of diabetic patients.

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