



# Importance of Observational Studies in Understanding Regional Clinical Practice: Rationale and Design of the A<sub>1</sub>chieve<sup>®</sup> Study

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## Introduction : Randomized controlled trials (RCTs) vs. Observational Studies

Randomized controlled trials (RCTs) are a necessary part of clinical research in diabetes. RCTs are necessary to establish treatment efficacy and safety; identify adverse events including tolerability issues; and identify approaches to optimal use of new medications. However, RCTs are performed on selected populations usually under more intensive clinical supervision. As a result they may not reflect situations in everyday clinical practice. An observational study can be defined as follows: “a study that provides estimates and examines associations of events in their natural settings without recourse to experimental intervention.” Observational studies have several advantages over RCTs, including lower cost, greater timeliness, and a broader range of patients. Concern about inherent bias in these studies, however, has limited their use in comparing treatments. Traditionally, observational studies have been used to identify risk factors and prognostic indicators when randomized, controlled trials would be difficult or unethical to conduct.<sup>1</sup>

Observational studies may provide information about the safety and effectiveness of treatment regimens with respect to the local standards of clinical care. They usually have minimal inclusion and exclusion criteria, so the heterogeneous populations enrolled tend to reflect the types of cases physicians see in their clinics. In contrast, the very purpose and design of RCTs require them to enrol very homogeneous populations and so, for example, they may exclude patients with common comorbidities or severe disease. Observational studies are non-interventional, so patients are prescribed a treatment according to their physician’s judgement or local clinical practice and receive only standard medical care. Again, this contrasts with

RCTs, where the enrolled subjects are treated as the treatment algorithms referred from the protocol and also receive intensive clinical support and follow-up. Therefore, while RCTs are essential to prove the safety and efficacy of drug therapies, observational studies provide valuable additional information about how therapies perform in real life (Figure 1).

## Observational Studies in Diabetes Mellitus

Observational studies typically play an important role in evaluating treatment outcomes, particularly in large, heterogeneous patient populations with complex, chronic diseases like diabetes mellitus. In these scenarios, the patients studied in RCTs may not be fully representative of the general patient population and hence, the results may lack generalizability. Understanding insulin therapy in patients with type 1 and 2 diabetes mellitus is an instance where the use of observational studies has found great significance. Diabetes is considered the “paradigm of chronic disease”, so it is relevant to consider the use of observational studies in this disease and therapeutic area. The nature of the RCT study design, like any, can bring drawbacks and challenges which leave gaps in the evidence base that observational studies are ideally suited to fill. Furthermore, observational studies offer a flexible approach and the two designs can be used together to provide complementary evidence.<sup>2</sup>

### Uses of Observational Studies in Diabetes

- Assess treatment effects (efficacy, safety, tolerability) in diverse patient groups in different clinical environments
- Evaluate current clinical practice to guide future guideline and resource development
- Provide data for health economic analyses (to help allocate health-care resources more efficiently)

Randomized clinical trial		Observational studies
Study population	Population	Representative clinical
Limited	Number of participants	Many
Restricted	Participant selection criteria	Broad
Phases 1-4	Regulatory phase	Phase 4 or later

Fig. 1 : From randomized controlled trials to “real life” understanding

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It has often been discussed that developing nations are particularly burdened by the increasing healthcare costs associated with diabetes. India is no exception and indeed we are struggling to afford the necessary resources to treat patients adequately compared to developed nations. There is a paucity of data in developing nations regarding treatment strategies, safety and efficacy of insulin use in real life clinical practice and health economic information. It is also important that the study should have adequate timelines to maximize follow-up by physicians and patients. Besides, health economic (HE) evaluation is not easy in diabetes. The rapid growth in prevalence of diabetes has put severe strain on healthcare systems in low and middle-income countries. Health economic evaluation of diabetes can be difficult due to the long disease duration and complexity of outcomes, among other factors.



Fig. 2 : A<sub>1</sub>chieve<sup>®</sup> enrolled a large and diverse population

- Multicentre, non-interventional, open-label, prospective observational study

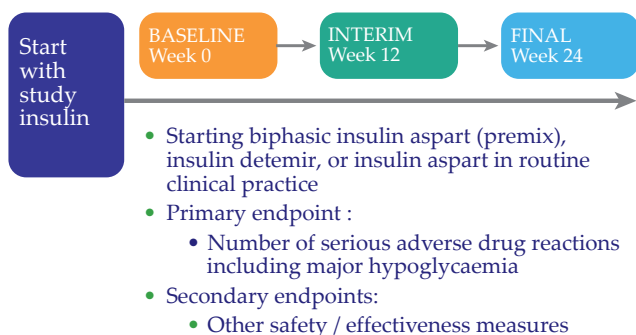


Fig. 3 : A<sub>1</sub>chieve<sup>®</sup> study design

## Rationale for the A<sub>1</sub>chieve<sup>®</sup> Study

It is widely accepted that well designed observational studies such as A<sub>1</sub>chieve<sup>®</sup> can help fill these information gaps and improve diabetes care. The A<sub>1</sub>chieve<sup>®</sup> study expands the knowledge and understanding of insulin analogue initiation/intensification, obtained through the 4T study, for daily practice in real life setting.<sup>3,4</sup> The 4T was a RCT to determine efficacy of different insulin regimens over a three year period. The study compared three types of insulin: basal insulin, given once (or twice) daily, prandial insulin, given three times daily, and biphasic insulin, given twice daily. The A<sub>1</sub>chieve<sup>®</sup> is akin to a “real-life” 4T study, where the data in routine clinical practice is captured to evaluate the safety and effectiveness of biphasic insulin aspart (BIAsp), insulin aspart (IAsp) and insulin detemir (IDet) alone or in combination in type 2 diabetes.<sup>3,4</sup> The country specific baseline data also provides relevant information on current diabetes management status, glycaemic control, complications, treatment practices, and patients’ (type 2 diabetes) quality of life in different countries, including India.

It is expected that the results from observational studies provide integral data for health economic analyses including medication usage patterns, current standards of care, and frequency of screening for diabetic complications.<sup>1,2</sup> Extensive prevalence, mortality and healthcare cost exist for emerging nations and insulin safety and effectiveness data from real-life clinical practice is limited in countries like India. These and related data are essential for effective diabetes management and also help address the “knowledge gap” alluded to. Besides, such studies in diabetes compare clinical practice standards in countries around the world, and simultaneously investigate the safety and effectiveness of various insulin regimens in regional clinical practice settings.<sup>3</sup> Figure 2 shows the large and diverse population enrolled in the A<sub>1</sub>chieve<sup>®</sup> study.

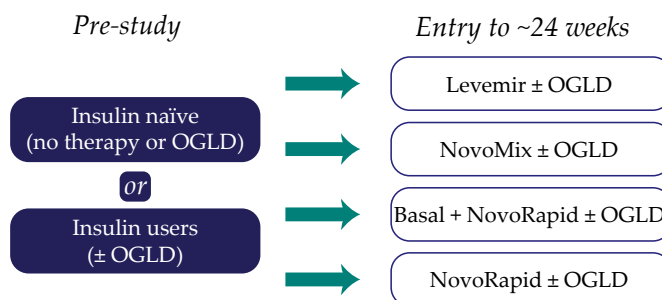


Fig. 4 : A<sub>1</sub>chieve<sup>®</sup> study design. OGLD, oral glucose lowering drugs

## Design of the A<sub>1</sub>chieve<sup>®</sup> Study

It had been already emphasized that the availability of global and local data across different countries and cultures will help us understand insulin therapy better. The A<sub>1</sub>chieve<sup>®</sup> was conceived to enable further consideration of the specific treatment groups in routine clinical practice to help define who might benefit the most from each regimen based on individual need. The study would also help define appropriateness of current diabetes care and provide “real-life” observational data to assess and improve clinical practice with guidance on insulin usage, while starting or optimizing insulin therapy.

The A<sub>1</sub>chieve<sup>®</sup> was an international, prospective, multi-centre, open label, non-interventional study of 24-week duration in people with T2DM starting BIAsp 30, IDet, or IAsp in routine clinical practice. The primary endpoint was the number of serious adverse drug reactions including major hypoglycaemia from baseline to end of trial. The secondary endpoints included other safety and effectiveness measures.<sup>3-5</sup>

Considering the non-interventional study design, insulin therapies were prescribed by a physician in the course of normal clinical practice. The inclusion of patients was at the discretion of the treating physician. The prescribing physician determined the choice of insulin; the starting dose and administration frequency, as well as later changes to either dose or frequency, if any. The protocol did not define any study related procedures or measurements and the data collected consisted of the parameters collected as part of the routine care. The safety and effectiveness of therapy were determined from measurements made at usual clinic visits and recorded from the clinicians’ notes and patients’ recall and diaries. The study design and treatment flow has been elaborated in the figures 3 and 4.

Globally, 3,166 investigators enrolled 66,726 people with T2DM in this study, making it the largest study in insulin therapy. The Indian cohort consisted of 621 investigators and 20,554 patients with T2DM. Informed consent, eligibility, baseline demographic data, medical history and the relevant diabetes treatment history were collected at the first visit. Weight, current diabetes treatment regimen, blood glucose control parameters, hypoglycaemia, adverse events and adverse drug reactions (AE and ADR) were recorded during the next two visits (interim? and final). Quality of life, as ascertained by the EQ5D self-rated questionnaire was recorded at baseline and at the final visits.<sup>4,5</sup> This special supplement discusses the results from the Indian cohort in great details.

It is widely anticipated that the data from A<sub>1</sub>chieve<sup>®</sup> will provide insight into diabetes care in clinical practice across the globe. It will also address questions like how do we compare to our neighbours; status of diabetes management across different countries, diabetes complications; and safety and effectiveness of

different insulin regimens in our local situation. Observational studies have certain inherent limitations like the lack of randomization, leading to potential for bias. Besides, if the data have been collected for a reason other than the observational study, it is unlikely that all relevant information will have been rigorously collected and there is potential for confounding variables. However, it must be emphasized that notwithstanding these limitations, observational studies usually do provide valid information and could be used to exploit the many recently developed, clinical data bases.<sup>6</sup> “Real-life” observational data is essential to assess and improve clinical practice worldwide and complement RCTs by providing clinically-relevant, real-world data and provide considerable health economic information to policy makers. With an average duration of diabetes 8.0 years and mean HbA1c of 9.5 % with 9% without any kind of diabetes treatment, the A<sub>1</sub>chieve<sup>®</sup> study re-emphasises the fact that there is significant delay in beginning or optimizing insulin therapy despite poor glycemic control.<sup>7</sup>

In the Indian cohort of 20554 people with type 2 diabetes, the mean HbA1c value was  $9.3 \pm 1.4$  and the average duration of diabetes was  $6.3 \pm 4.6$  years. More than 75% of the participants were being treated with oral glucose lowering drugs (OGLD) alone despite poor glycaemic control. Neuropathy (24.6%) and cardiovascular disease (23.6%) were the most common complications prevailing in the Indian cohort of A<sub>1</sub>chieve<sup>®</sup> participants at baseline. The final results conclude that significant HbA1c reductions on all study insulins (1.9% HbA1c reduction in insulin naïve patients; 1.7% HbA1c reduction in insulin users). Approximately 23% of Indian patients achieved HbA1c <7.0% with low rates of hypoglycaemia on all study insulins with no significant weight change observed in all treatment subgroups.

Self-rated health was good on all study insulins after week 24. The global results of the study have been published earlier<sup>5,7</sup> and in this supplement we discuss the results of the Indian cohort in greater details. In summary, this study highlights there are unmet needs in the management of type 2 diabetes in India is a constant need to improve the management of type 2 diabetes.

## References

1. Black N. Why we need observational studies to evaluate the effectiveness of health care. *BMJ* 1996;312:1215–18.
2. Ligthelm RJ, Borzi V, Gumprecht J, Kawamori R, Wenyng Y, Valensi P. Importance of observational studies in clinical practice. *Clin Ther* 2007;29:1284–92.
3. Shah SN, Litwak L, Haddad J, Chakkarwar PN, Hajjaji I. The A<sub>1</sub>chieve<sup>®</sup> study: a 60,000-person, global, prospective, observational study of basal, meal-time, and biphasic insulin analogs in daily clinical practice. *Diabetes Res Clin Pract* 2010;88:S11–6.
4. Holman RR, Farmer AJ, Davies MJ, Levy JC, Darbyshire JL, Keenan JF, et al. Three-year efficacy of complex insulin regimens in type 2 diabetes. *N Engl J Med* 2009;361:1736–47.
5. Shah S, Zilov A, Malek R, Soewondo P, Bech O, Litwak L. Improvements in quality of life associated with insulin analogue therapies in people with type 2 diabetes: results from the A<sub>1</sub>chieve observational study. *Diabetes Res Clin Pract* 2011;94:364–70.
6. Benson K, Hartz JA. A comparison of observational studies and randomized, controlled trials. *N Engl J Med* 2000;342:1878–86.
7. Home P, Naggar NE, Khamseh M, Gonzalez-Galvez G, Shen C, Chakkarwar P, et al. An observational non-interventional study of people with diabetes beginning or changed to insulin analogue therapy in non-Western countries: the A<sub>1</sub>chieve<sup>®</sup> study. *Diabetes Res Clin Pract* 2011;94:352–63.