

# Investigation of Regimen Adjustment for T2DM Patients Inadequately Controlled on Basal Insulin – Interpretation of the 4200 Study

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## Abstract

The 4200 study is a randomized controlled trial, aimed to confirm the efficacy and safety of BIAsp 30 BID or TID in T2DM patients inadequately controlled on basal insulin, with 69% of the subjects recruited from mainland China. After 24 weeks of treatment, HbA1c level decreased comparably and hypoglycemia rates were similar between BIAsp BID and BIAsp TID groups. This study provided new evidence and inspiration for drug options in regimen adjustment for Chinese T2DM patients inadequately controlled on basal insulin.

**Keywords:** T2DM, BIAsp 30, Insulin regimen switch

## Background

Epidemiological survey indicated that majority of Chinese T2DM patients were with postprandial hyperglycemia [1], which may be related to more significant decline of  $\beta$  cell function and more carbohydrates in dietary structure [2]. Thus, antidiabetic interventions for Chinese T2DM patients should rectify hyperglycemia as soon as possible to protect  $\beta$  cell function, and the treatment should cover both fasting and postprandial blood glucose.

Results from real-world studies [3-4] indicated that the proportion of patients achieving HbA1c < 7.0% was less than 40% after 3 months of basal insulin treatment, and prolonged basal insulin therapy was associated with slowed HbA1c reduction and increased hypoglycemic risk. 4T study [5] suggested that 81.6% of the patients who initiated basal insulin needed to add prandial insulin to achieve glycaemic target after 3 years. CREDIT study [6] showed that more than 80% patients who initiated basal insulin added prandial insulin in real-world setting.

Biphasic insulin aspart 30/70 (BIAsp 30) launched in

China in 2005. The efficacy and safety of BIAsp 30 in Chinese population has been demonstrated by many large sample size randomized controlled studies and real-world studies including 1707 [7], PRESENT [8], IMPROVE™ [9], A1chieve® [10], INTENSE [11] during these 15 years, suggesting BIAsp30 as a suitable insulin therapy for Chinese diabetes patients. BIAsp 30 twice daily is a classic regimen. An observational study ‘The 1-2-3 study’ [12] suggested that the rate of achieving HbA1c goals was improved without significantly increasing hypoglycemic episodes (major, minor and nocturnal hypoglycemic events) for patients inadequately controlled (HbA1c > 6.5%) on BIAsp once daily regimen by increasing the injection frequency to twice or thrice daily.

The Chinese subgroup analysis of a global real-world study ‘the A1chieve study [10]’ showed that, HbA1c was reduced by 1.9% and hypoglycemic rate was significantly decreased when T2DM patients inadequately controlled on basal insulin switching to BIAsp 30 twice daily. And the 4200 study is the first randomized controlled trial to investigate the efficacy and safety of BIAsp 30 twice daily (BID) or three times daily (TID) in T2DM patients

inadequately controlled on basal insulin.

## Design and Results

The 4200 study [13] is a 24-week, multinational, randomized, open-label, parallel controlled, treat-to-target trial. Subjects inadequately controlled (HbA1c 7.5-10.0%) on basal insulin and metformin  $\pm$  1 oral antidiabetic drugs (OADs) were randomized to BIAsp 30 TID (n=220) or BIAsp 30 BID (n=217), among which 69.0% were from mainland China and over 78% were using insulin glargine at baseline. After 24 weeks of treatment, HbA1c decreased comparably in both groups (-1.6% vs. -1.7% for BIAsp BID and BIAsp TID groups respectively; p=0.26). The hypoglycemia event rates were similar and the number of severe hypoglycemic episodes was low. Both regimens were safe and well-tolerated.

## Discussion

T2DM patients inadequately controlled on basal insulin could switch to basal-bolus, premix insulin or CSII regimen [14]. Meta-analysis [15] indicated that HbA1c reduction and the hypoglycemia rates were similar between basal-bolus and premix insulin regimens. However, basal-bolus regimens are relatively complex, thus associated with higher likelihood of dose missing or medication errors [16,17]. The 4200 study demonstrated that the efficacy and safety were similar when T2DM patients inadequately controlled on basal insulin switching to BIAsp 30 BID or TID. During clinical practice, adding a third injection of BIAsp 30 at lunchtime may be preferable if HbA1c remains above target, if the lunchtime meal is the largest meal of the day, or if there is persistent postprandial hyperglycemia after lunch, based on individual features of patients by discretion of clinicians. The 4200 study provided new evidence for Chinese T2DM patients inadequately controlled on basal insulin switching to BIAsp 30, offering more options for further optimization when basal insulin failed.

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