



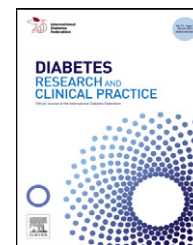
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Switching from biphasic human insulin 30 to biphasic insulin aspart 30 in type 2 diabetes is associated with improved glycaemic control and a positive safety profile: Results from the A₁chieve study

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ABSTRACT

Aims: This A1chieve® study subgroup analysis examined clinical safety and effectiveness of biphasic insulin aspart 30 (BIAsp30) ±OGLDs in 6323 individuals with T2D, switching from biphasic human insulin 30 (BHI30) ±OGLDs.

Methods: A1chieve was a 24-week, international, prospective, observational, multi-centre, open-label study in individuals with T2D starting treatment with BIAsp30, insulin detemir or insulin aspart as part of routine clinical care.

Results: Mean baseline (SD) dose BHI was 0.56 (0.25) IU/kg. BIAsp30 was initiated at 0.57 (0.25) U/kg; the daily dose was 0.62 (0.28)U/kg by Week 24. Switching from BHI30 to BIAsp30 was associated with significant mean reduction in HbA_{1c} of 1.7% [–18 mmol/mol] (1.6) from a baseline of 9.1% [76 mmol/mol] ($p<0.001$); FPG and PPG were also significantly reduced ($p<0.001$). Major hypoglycaemic episodes decreased from 0.69 events/patient/year at baseline to 0.03 events/patient/year at Week 24. Minor hypoglycaemia decreased from 5.31 to 2.04 events/patient/year from baseline to study-end. Five serious adverse drug reactions (hypoglycaemia) were reported by five individuals (0.1%). Mean bodyweight increased by 0.1 (3.3)kg from baseline to 24 weeks. Improved self-reported quality of life was observed.

Conclusion: Switching from BHI30 to BIAsp30 in individuals with T2D is associated with improvement in glycaemic control and reduced rates of hypoglycaemia, without tolerability or safety issues.

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1. Introduction

Biphasic insulin preparations provide a convenient way to address both basal and prandial glucose-lowering needs, as they provide both intermediate and rapid/short-acting insulin components in a single injection. Biphasic insulin preparations therefore provide the possibility of a simple approach to address both fasting plasma glucose (FPG) and post-prandial plasma glucose (PPG), which has been shown to be important in order to achieve glycated haemoglobin (HbA_{1c}) targets [1,2]. PPG has also been identified as an independent risk factor for diabetic complications such as cardiovascular disease [3]. Therefore, clinical guidelines such as those published by the International Diabetes Federation recommend targeting both FPG and PPG at all HbA_{1c} levels in order to achieve glycaemic targets, and to minimise the development of diabetic complications [4].

Biphasic insulin analogue preparations offer a number of advantages over biphasic human insulin (BHI). Biphasic insulin aspart 30 (BIAsp 30; NovoMix[®] 30, Novo Nordisk) has been shown to provide better control of PPG than BHI 30 in a meta-analysis including data from nine randomised controlled trials (RCTs) in patients with Type 2 diabetes mellitus (T2D) [5]. The same meta-analysis also demonstrated that BIAsp 30 was associated with a 50% lower rate of major hypoglycaemia and a 55% lower rate of nocturnal hypoglycaemia compared with BHI 30. However, there was a 24% higher risk of daytime hypoglycaemia with BIAsp 30 compared with BHI 30.

In addition to data from RCTs, observational studies such as IMPROVE[™] and the Physicians' Routine Evaluation of Safety and Efficacy of NovoMix[®] 30 Therapy (PRESENT) study demonstrated that switching from BHI 30 to BIAsp 30 is associated with improved glycaemic control and a reduced risk of hypoglycaemia [6,7]. It is important to select insulin therapy according to individual needs and the A₁chieve[®] study is the first observational study that included individuals who were switched to BIAsp 30, insulin detemir (Levemir[®], Novo Nordisk) or insulin aspart (NovoRapid[®], Novo Nordisk) alone or in combination as part of their routine clinical care [8]. The aim of this subgroup analysis of the A₁chieve[®] study was to examine data regarding the clinical safety and effectiveness of BIAsp 30 ± oral glucose-lowering drugs (OGLDs) in people with T2D when switching from their previous treatment of BHI 30 ± OGLDs.

2. Materials and methods

2.1. Study design

The A₁chieve[®] study was an international prospective, observational, multicentre, open label, non-interventional, 24-week study in people with T2D who were treatment naïve or who had been using anti-diabetic medication other than Novo Nordisk insulin analogues being evaluated and who had started treatment with BIAsp 30, insulin detemir or insulin aspart (alone or in combination) in routine clinical practice [8]. This subgroup analysis examined the effects of switching from BHI 30 to BIAsp 30.

2.2. Setting

The A₁chieve[®] study was performed in 28 countries in seven regions (China, South Asia, East Asia, North Africa, Middle East/Gulf, Latin America and Russia) between November 2008 and March 2011. This manuscript reports overall data and individual regional data for five of the seven regions.

2.3. Participants

Patient selection was at the discretion of the individual physician. After the physician had taken the decision to use BIAsp 30, insulin detemir or insulin aspart (alone or in combination), any patient with T2D who was not treated with the insulin analogues being evaluated (or who had started on these insulin analogues within the last 4 weeks before inclusion into this study) was eligible for the study. Individuals who had a hypersensitivity to the insulin analogues being evaluated and women who were pregnant, lactating or had the intention of becoming pregnant within the next 6 months were excluded. Ethics committee approval was gained in each country. Each participant provided written informed consent.

2.4. Variables

The efficacy variables included changes in HbA_{1c}, FBG and PPG at Weeks 12 and 24 compared with baseline. Change in quality of life (QoL) from baseline to Week 24 was also examined.

The primary safety variable was the number of serious adverse drug reactions (SADRs) including major hypoglycaemic events from baseline to final visit. Secondary safety variables included change in number of hypoglycaemic events and nocturnal hypoglycaemic events in the 4 weeks prior to the interim and final visit compared with the 4 weeks prior to the baseline visit; the number of adverse drug reactions (ADRs) from baseline to final visit; and change in body weight at Weeks 12 and 24 compared to baseline. Other secondary safety assessments were adverse events (AEs), and change in lipids and creatinine at Week 24 compared with baseline.

2.5. Data sources/measurement

The most recent measurements taken during the 4 weeks prior to each visit were recorded for HbA_{1c}, FPG and PPG values at baseline, Week 12 and Week 24. ADRs and serious AEs (SAEs) were collected and reported. At each contact with their physician (visit or telephone), participants were questioned about ADRs and a case report form was completed whenever an event was reported. Participants were asked to complete the EQ-5D questionnaire, a validated tool used to assess QoL at baseline and Week 24. The questionnaire covered five areas: mobility, self care, usual activities, pain/discomfort and anxiety/depression. The EQ-5D questionnaire also enabled individuals to rank their QoL based on a visual analogue scale (0–100) where 100 corresponds to the highest QoL.

2.6. Study size

Physicians could choose to start individuals on BIAsp 30, insulin detemir or insulin aspart alone or in combination.

Assuming an equal distribution of people amongst these insulins, a sample size of 60,000 people was calculated to be sufficient to detect an SADR with an incidence of 0.015%.

2.7. Statistical methods

Changes from baseline for HbA_{1c}, FPG, PPG, lipids and QoL were analysed using a paired t-test. For the purposes of this publication the cut-off for reporting individual regional data was set at <100 people. Therefore, data for Latin America (40 individuals) and Russia (86 individuals) are not reported individually, but data from these patients are included in the overall cohort. The majority of data are expressed as mean (standard deviation [SD]) unless otherwise stated.

3. Results

3.1. Population disposition

A total of 66,726 patients participated in A₁chieve[®], of which 6323 switched their insulin therapy from BHI 30 ± OGLDs to BIAsp 30 ± OGLDs. There were 991 withdrawals (15.7%) from this group (585 individuals lost to contact, 401 for other reasons [including ‘investigator dropout’ in 120 cases and ‘pages not retrievable’ in 163 cases] and five due to ADRs). Therefore, 5332 people completed the study. The efficacy analysis set (EAS), which included all individuals with at least one measurement of FPG, PPG, most recent HbA_{1c}, weight or hypoglycaemic events at baseline and final visit and who maintained the same study insulin during the study, comprised 5200 people. A total of 1123 individuals were excluded from the EAS due to missing endpoint data at baseline and/or final visit (n=991) and/or not maintaining BIAsp 30 treatment throughout the study (n=148).

3.2. Baseline characteristics

Of the 6323 individuals who started on BIAsp 30, 56.9% were male. The mean age was 55.4 years and diabetes duration was 11.1 years. Mean duration on insulin therapy was 3.3 years. Mean body mass index (BMI) was 27.3 kg/m² and mean body weight was 74.0 kg (Table 1). There were regional differences, particularly in bodyweight and BMI. The subgroup included a proportion of individuals with various diabetic complications

including cardiovascular (33.3%), renal (36.9%), eye (35.7%), foot ulcer (6.1%) and neuropathy (49.7%) at baseline.

3.3. Insulin dose and dosing frequency

The mean BHI 30 dose at baseline was 0.56 (0.25) IU/kg. The mean BIAsp 30 dose at baseline was 0.57 (0.25) U/kg, and increased to 0.62 (0.28) U/kg by the end of study (Week 24). The majority of individuals (89.5%) across all regions were on prior twice-daily BHI 30 treatment. At baseline and Week 24, 86.6% and 84.6% of patients received twice-daily BIAsp 30, respectively. A total of 4.5% of patients were administered once-daily BIAsp 30 at both baseline and Week 24; while 8.8% and 10.0% of patients were administered three-times daily BIAsp 30 at baseline and Week 24, respectively.

3.4. Glycaemic control

Switching from BHI 30 to BIAsp 30 was associated with a significant mean reduction [SD] in HbA_{1c} of 1.7% [−18 mmol/mol] (1.6) from a baseline of 9.1% [76 mmol/mol] (1.7) ($p < 0.001$; Figure 1). At baseline, 373 (6.9%) of individuals who had previously used BHI 30 had an HbA_{1c} <7% [53 mmol/mol]. By Week 24 following the switch to BIAsp 30, 1520 (33.6%) of individuals had an HbA_{1c} <7% [53 mmol/mol] ($p < 0.0001$). FPG was also significantly reduced by 3.0 (3.5) mmol/l from a baseline of 10.2 (3.4) mmol/l ($p < 0.001$; pre-breakfast data shown in Figure 2). PPG following breakfast was significantly reduced in the overall population and in individual countries by Week 24 versus baseline (Table 2). Comparable PPG reductions from baseline to Week 24 were also observed in post-lunch PG (−4.5 [4.2] mmol/l) and post-dinner PG (−3.7 [3.7] mmol/l) in the overall group ($p < 0.001$ for both reductions).

3.5. Hypoglycaemia

The rate of major hypoglycaemic episodes decreased from 0.69 events per patient year at baseline to 0.03 events per patient year by the end of the study. The rate of minor hypoglycaemic episodes decreased from 5.31 to 2.04 events per patient year from baseline to the end of the study. In total, 335 major hypoglycaemic episodes at baseline were reported by 224 individuals (3.5%), 216 diurnal episodes were reported by 170

Table 1 – Baseline characteristics of individuals who switched from biphasic human insulin 30 to biphasic insulin aspart 30.

Parameter	Total cohort	China	South Asia	East Asia	North Africa	Middle East/Gulf
N	6323	1191	2210	650	512	1634
Male, N (%)	3588 (56.9)	655 (55.0)	1442 (65.3)	340 (52.3)	219 (42.8)	899 (55.4)
Mean age, years (SD)	55.4 (12.5)	57.5 (15.5)	54.8 (10.7)	56.3 (11.4)	57.1 (12.2)	53.2 (12.5)
Mean body weight, kg (SD)	74.0 (14.8)	68.8 (10.9)	70.1 (11.4)	66.6 (13.1)	77.8 (13.2)	84.9 (16.3)
Mean BMI, kg/m ² (SD)	27.3 (5.1)	25.0 (3.2)	26.1 (3.9)	25.5 (4.6)	29.2 (5.4)	31.1 (5.8)
Mean duration of T2D, years (SD)	11.1 (6.6)	10.6 (6.6)	10.1 (5.3)	10.4 (7.7)	12.4 (7.7)	12.5 (6.9)
Mean time to insulin initiation, years (SD)	7.3 (5.4)	7.4 (5.9)	7.1 (4.4)	7.5 (6.6)	7.2 (6.2)	7.5 (5.3)
Mean duration on insulin therapy, years (SD)	3.3 (3.3)	3.4 (3.2)	3.0 (2.6)	2.8 (3.1)	5.2 (5.2)	5.1 (4.7)
Mean HbA _{1c} , % (SD) [mmol/mol]	9.1 (1.7) [76]	8.7 (2.1) [72]	9.1 (1.4) [76]	9.5 (1.9) [80]	9.0 (1.6) [75]	9.4 (1.8) [79]

BMI, body mass index; SD, standard deviation

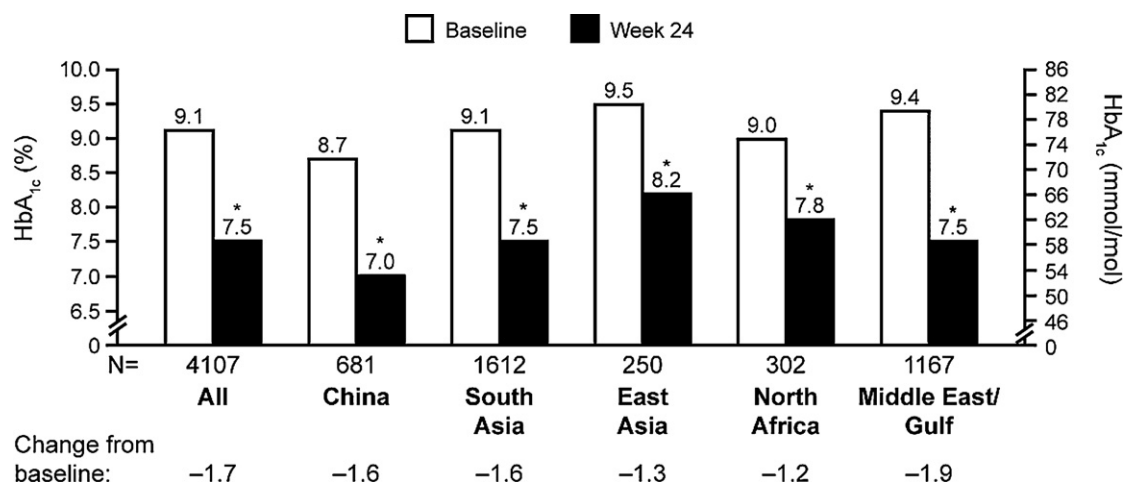


Fig. 1 – Mean HbA_{1c} reductions in the overall group and by region. *p<0.001.

individuals (2.7%) and 119 nocturnal episodes were reported by 95 individuals (1.5%). At the end of 24 weeks, four individuals (0.08%) reported 12 major hypoglycaemic episodes including seven diurnal episodes reported by three individuals (0.06%) and five nocturnal episodes reported by two individuals (0.04%). A total of 1042 (16.5%) of individuals reported 2584 minor hypoglycaemic episodes at baseline. By Week 24, 424 individuals (8.0%) reported 838 minor hypoglycaemic episodes.

3.6. Serious adverse drug reactions

Five SADR (hypoglycaemia) were reported by five patients (0.1%); two in the North Africa and three in the Middle East/Gulf regions. Twenty-two individuals (0.3%) reported 24 SAEs. These included seven hypoglycaemic events, four cardiac disorders (two congestive cardiac failures, one cardiogenic shock and one myocardial infarction), three gastrointestinal disorders (one abdominal pain, one diarrhoea and one vomiting), three infections (two lung and one streptococcal

septic arthritis), three malignant neoplasms, one chronic renal failure, one respiratory failure, one neuropathic ulcer and one angioplasty. Relationship to study drug was assessed as unlikely for 19 events, possible for one event (hypoglycaemia) and probable for four events (hypoglycaemia). SAEs were assessed as severe (11), moderate (10) or mild (3).

3.7. Bodyweight

Overall, there was an increase in bodyweight of 0.1 (3.3) kg from baseline to Week 24 (China +0.5 kg, South Asia 0 kg, East Asia +0.6 kg, North Africa +0.5 and Middle East/Gulf -0.4 kg).

3.8. Quality of life

An improvement in QoL (SD) was observed from a baseline of 64.0 (16.3) to 76.5 (11.9) at the end of study as measured by a visual analogue scale 0–100 with 0=worst and 100=best imaginable health state.

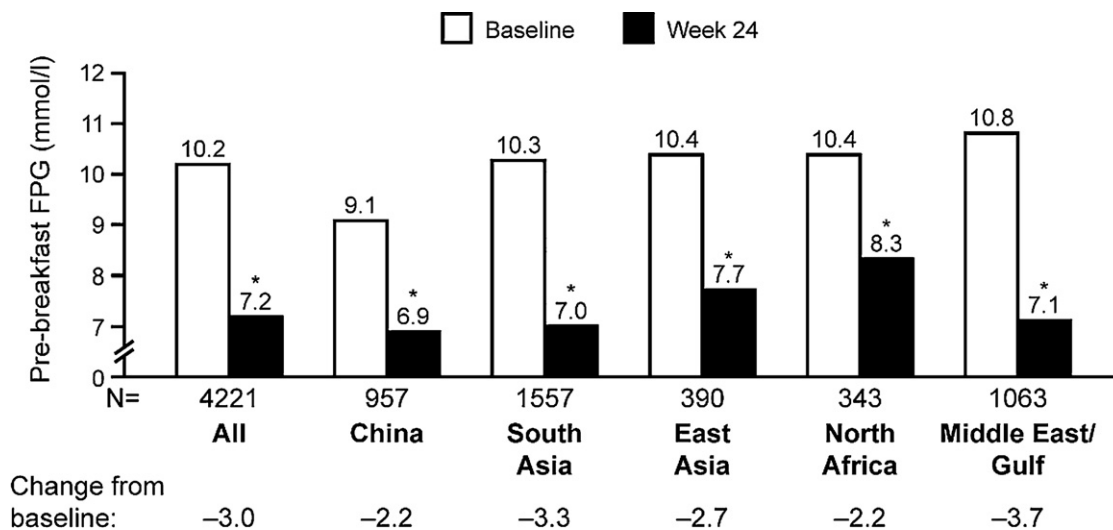


Fig. 2 – Mean pre-breakfast FPG reductions in the overall group and by region. *p<0.001. FPG, fasting plasma glucose.

Table 2 – Post-breakfast plasma glucose reductions in the overall group and by region.

N	All 2961	China 722	South Asia 1009	East Asia 239	North Africa 198	Middle East/Gulf 724
Post-breakfast PG (mmol/l), mean (SD)						
Baseline	14.2 (4.3)	12.9 (4.2)	15.1 (3.9)	14.7 (4.8)	14.1 (4.3)	14.3 (4.4)
Week	24 9.9 (2.8)	9.1 (2.0)	10.8 (3.2)	10.3 (3.4)	10.2 (2.8)	9.2 (2.4)
Change from baseline	-4.3 (4.3)	-3.8 (4.3)	-4.4 (4.0)	-4.3 (5.2)	-3.9 (4.9)	-5.0 (4.2)
[P-value]	[<0.001]	[<0.001]	[<0.001]	[<0.001]	[<0.001]	[<0.001]

PG, plasma glucose; SD, standard deviation

3.9. Reasons for changing therapy

The most common reason for switching to BIAsp 30 was to improve glycaemic control (91.4%). Other reasons were: to try a new insulin (35.3%), to reduce the risk of hypoglycaemia (34.3%), to reduce PG variability (29.3%) and dissatisfaction with current therapy (26.0%).

4. Discussion

Switching from BHI 30 to BIAsp 30 was associated with significant improvements in HbA_{1c}, FPG and PPG combined with a reduction in the rates of major and minor hypoglycaemia. The numbers of reported SADR and SAEs were low. Overall, there was a negligible increase in mean bodyweight over the 24 weeks. Insulin dose increased slightly from baseline to Week 24. Switching to BIAsp 30 was also associated with improved self-reported QoL.

Observational studies can provide important clues about how drugs perform under conditions of real-life clinical practice. The results presented here confirm that switching from BHI 30 to BIAsp 30 is associated with significant reductions in PPG in a real-life setting. This supports results from RCTs that have consistently shown significantly better PPG reductions for BIAsp 30 compared with BHI [9–11]. This improvement in PPG may reflect the earlier and higher peak postprandial insulin concentrations achieved by BIAsp 30 compared with BHI 30 [12].

It is important to address PPG control in order to achieve HbA_{1c} targets [1,2]. In addition, lowering PPG is associated with reduced cardiovascular risk [3]. Failure to control PPG has been independently associated with macrovascular disease, retinopathy, cancer, impaired cognitive function in the elderly, increased carotid intima-media thickness, decreased myocardial blood volume and myocardial blood flow and oxidative stress, inflammation and endothelial dysfunction in individuals with diabetes [4]. Baseline data from this study show that post-breakfast PPG was in the range of 12.9–15.1 mmol/l depending on region, well above the IDF recommended PPG target of <9 mmol/l [4]. However, following 24 weeks of BIAsp 30 treatment, mean PPG was 9.9 mmol/l, a 4.3 mmol/l improvement, although still above the IDF target.

In this study BIAsp 30 was also associated with significant improvements in FPG versus BHI although this finding has not been demonstrated by clinical trials [5,13]. Similarly, clinical trials have failed to demonstrate improved HbA_{1c} reductions with BIAsp 30 over BHI [5,13,14]. The data from clinical trials

are in contrast to the impressive HbA_{1c} improvements observed in this study of between 1.2 and 1.9%. It is possible that A₁chieve[®] provided a stimulus for improved diabetes management or the adoption of positive lifestyle changes. This hypothesis was supported by the overall A₁chieve[®] data, which showed minimal body weight gain in association with improved HbA_{1c}, as well as improved blood pressure and lipid profile [8]. It should be noted that there was an increase in the daily insulin dose from baseline to the end of study that may explain the improvements in glycaemic control.

The rate of major and minor hypoglycaemic episodes was reduced from baseline to week 24 in this study. Significant reductions in major and nocturnal hypoglycaemia were also observed in a meta-analysis of trials comparing BIAsp 30 and BHI [5]. A crossover study by McNally *et al* 2007 employed continuous glucose monitoring to examine the frequency of low interstitial glucose values in individuals treated with BIAsp 30 or BHI 30 [12]. The study demonstrated an increased frequency of nocturnal low glucose values with BHI 30 versus BIAsp 30 and this was associated with higher rates of self-reported nocturnal hypoglycaemia with BHI 30.

The A₁chieve[®] study has a number of limitations that should be considered when assessing these results. It is a multinational noninterventional study and as such it is subject to the heterogeneity of healthcare systems in individual countries. Non-interventional studies do not have tightly controlled populations or control groups, which reduces the certainty with which outcomes can be ascribed to treatment. The incidence of hypoglycaemia at baseline was based on participants' recall of the past 4 weeks prior to the study visit. Therefore, there was some potential for recall bias, which might have resulted in an underestimate of the real incidence of minor hypoglycaemic episodes. However, data from this noninterventional study forms part of the evidence base alongside that from a comprehensive programme of controlled clinical trials.

A number of limitations of the A₁chieve[®] study design identified above, such as the lack of tightly controlled populations and the possible heterogeneity of diabetes care in different regions, mean that the study closely reflects 'real-life' clinical practice. The lack of strict inclusion/exclusion criteria meant that individuals who may have been excluded from more strictly controlled clinical trials were included in A₁chieve[®] study. Hence, it is likely that the enrolled population in A₁chieve[®] study closely reflected the wider population of individuals with diabetes in the regions studied. In addition, all clinical decisions were made by the treating physician, so although as a result, treatment heterogeneity was introduced

into the study, the findings accurately reflect ‘real-life clinical practice’. In addition, the fact that switching from BHI 30 to BIAsp 30 improved clinical outcomes in all regions despite potential differences in treatment approach suggests that the clinical effects observed could be achievable within a range of healthcare systems.

This study demonstrated that switching to BIAsp 30 treatment in individuals with T2D previously treated with BHI 30 was associated with improvements in glycaemic control and a reduction in major and minor hypoglycaemic episodes. Low numbers of SADR or SAEs were experienced by patients treated with BIAsp 30.

Conflict of interest

Dr El Naggar, Dr Soewondo, Dr Khamseh and Dr Haddad are on an advisory panel for Novo Nordisk. Dr Haddad is also a speaker for Novo Nordisk. Dr Chen is employed by Novo Nordisk.

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