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RESEARCH ARTICLE

Comparative efficacy and safety of two insulin aspart formulations (Rapilin and NovoRapid) when combined with metformin, for patients with diabetes mellitus: a multicenter, randomized, open-label, controlled clinical trial

Jun Yao[a], Xiaohui Guo[a], Li Sun[b], Ping Han[c], Xiaofeng Lv[d], Xiuzhen Zhang[e], Zhaohui Mo[f], Wenying Yang[g], Lihui Zhang[h], Zhanjian Wang[i], Lvyun Zhu[j], Quanmin Li[k], Tao Yang[l], Wenbo Wang[m], Yaoming Xue[n], Yongquan Shi[o], Juming Lu[p], Yongde Peng[q], Fan Zhang[r], Dewen Yan[s], Damei Wang[t] and Xuefeng Yu[u]

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ABSTRACT

Objective: This phase 3 confirmatory diabetes mellitus treatment study compared the safety and efficacy of Rapilin and NovoRapid insulin asparts in combination with metformin.

Methods: This 24-week, open-label, randomized, active-controlled, noninferiority phase 3 confirmatory study conducted across centers in China aimed to enroll patients with type 2 diabetes mellitus and blood sugar glucose inadequately controlled by oral antidiabetic drugs. Randomized patients received subcutaneous mealtime Rapilin or NovoRapid (3:1) injections, with metformin. The primary objectives were to demonstrate noninferiority (margin of 0.4%) in HbA1c change from baseline and compare safety profiles of Rapilin versus NovoRapid after 24 weeks. Secondary outcomes included 2-h postprandial plasma glucose (PPG), fasting plasma glucose (FPG), and patients achieving HbA1c $<7.0\%$ and $\leq 6.5\%$.

Results: 590 patients with type 2 diabetes mellitus were randomized to Rapilin ($n = 441$) and NovoRapid ($n = 149$) groups. After 24 weeks, the mean HbA1c change from baseline was -2.20% (Rapilin) and -2.32% (NovoRapid); the estimated treatment difference based on least-square means was 0.04% (95% CI: -0.17, 0.26), meeting the noninferiority criteria for Rapilin versus NovoRapid. Comparable improvements were reported for mean 2-hour PPG (6.14 and 6.29 mmol/L), FPG (2.02 and 1.70 mmol/L), and patients with HbA1c $<7.0\%$ (52.6% and 51.0%) and $\leq 6.5\%$ (34.2% and 30.9%), in the Rapilin and NovoRapid groups, respectively, with no significant safety or immunogenicity outcome differences.

Conclusions: Rapilin demonstrated non-inferior glycemic control, and matching safety and immunogenicity to NovoRapid in patients with type 2 diabetes mellitus also receiving metformin over 24 weeks.

Trial registration: ChiCTR20003129041

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KEYWORDS
Clinical trial; diabetes mellitus; efficacy; insulin aspart; NovoRapid; Rapilin

Introduction

The prevalence of diabetes mellitus in China has risen from 1% in 1980 to over 10% as of 2019, making it the highest in the world (with 116.4 million cases) and type 2 accounts for approximately 90% of these cases[1,2]. Subcutaneous insulin formulations are important treatment options for patients with diabetes mellitus, forming the core of treatment for patients with type 1 diabetes, and frequently being combined with metformin in patients with type 2 diabetes who have been unable to attain the target blood glucose levels with concomitant oral glycemic control medications[3–5].

Over the last few decades, specialized insulin analogs have been developed by altering the amino acid structure of

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Table 1. The pharmacological characteristics of Rapilin and NovoRapid.

PK/PD parameters	Rapilin	NovoRapid
$T_{1/2}$ (h)	0.774 ± 0.235	0.790 ± 0.261
T_{max} (h)	1.250 ± 0.691	1.360 ± 0.649
C_{max} (ng/L)	4103.1 ± 950.5	4197.4 ± 1049.6
$AUC_{(0-2h)}$ (h*ng /L)	5457.2 ± 132.1	5576.7 ± 1483.7
$AUC_{(0-12h)}$ (h*ng /L)	10,697.8 ± 1999.2	10,999.4 ± 2111.2
$AUC_{(0-inf)}$ (h*ng /L)	10,702.7 ± 2004.0	11,008.9 ± 2118.9
λ_z (1/h)	0.9679 ± 0.2637	0.9686 ± 0.3076
$AUC_{GIR.0-12}$ (mg/kg)	2638.7 ± 913.0	2598.1 ± 753.2
AUCmax (mg/kg/min)	9.969 ± 3.364	9.589 ± 3.158

Abbreviations. λz, terminal elimination rate constant; AUC, area under the curve; C_{max}, maximum concentration; GIR, glucose infusion rate; PD, pharmacodynamics; PK, pharmacokinetics; SD, standard deviation; $T_{1/2,}$ elimination half-life; T_{max}, time to maximum concentration. Data presented as Mean ± SD.

recombinant human insulin to provide additional benefits in terms of stability and speed of action[3]. Insulin aspart, a rapid-acting insulin analog, has an amino acid substitution at position B28 (proline substituted with aspartic acid)[6]. This substitution decreases insulin hexamer formation and promotes depolymerization, resulting in peak glucose infusion rates that are higher and occur earlier compared with human insulin, allowing administration immediately before a meal[7,8]. Typical onset of action for insulin aspart is 10–30 min following administration, with peak efficacy at 1–2 h and duration of effect of 3–6 h[8,9]. Most commonly, fast-acting analogs are administered using insulin pens, but can also be given *via* syringe and insulin pumps[3]. Treatment with rapid-acting insulin analogs, including insulin aspart, leads to improved blood glucose management without increasing the rate of hypoglycemia. However, the expense of currently available insulin analogs can be prohibitive for many patients, particularly in middle and lower-income countries[3,10].

Fast-acting insulin analogs, such as insulin aspart, are often used as part of a multiple dose insulin (MDI) therapy regimen, in combination with a long-acting (basal) insulin[3]. Indeed, the evidence supporting the efficacy of insulin aspart when used as insulin therapy in combination with oral glucose-lowering drugs, such as metformin, is limited to noninterventional and small crossover studies[8,11,12]. The studies that have been conducted suggest that patients receiving insulin aspart as the only insulin therapy experience improvements in glycemic control greater than human insulin treatment including better control of postprandial hyperglycemia[11,13], and reduced hypoglycemic event rates compared with their prior insulin regimens[12].

At the time the trial took place, Rapilin[i] (Gan & Lee Pharmaceuticals Co Ltd, Beijing, China) was classed as domestic insulin in China, registered and approved as a 'type 15: the biological product that already has the National Drug Standard'. In a previously described bioequivalence study ($n = 36$), Rapilin demonstrated pharmacokinetic and pharmacodynamic properties to match those of insulin aspart NovoRapid[ii] (Table 1)[14]. NovoRapid has been authorized for the treatment of patients with type 1 and type 2 diabetes mellitus across many countries since 1999[8,15].

We report the outcomes of the phase 3 confirmatory study comparing the safety and efficacy of Rapilin and NovoRapid, in combination with metformin, for the treatment of type 2 diabetes mellitus. To our knowledge, this is the first large-scale randomized controlled trial to investigate the use of insulin aspart in combination with metformin, without the use of basal insulin.

Methods

Trial design

This was a multicenter, randomized, open-label, active-controlled, noninferiority phase 3 confirmatory study to assess the efficacy and safety of Rapilin compared with NovoRapid in combination with metformin. Patient recruitment commenced in March 2013 and the last patient completed the trial in December 2014. The trial consisted of a 2-week screening period and a 24-week treatment period and was conducted across 21 centers in China.

Patients were randomized 3:1, without stratification, to receive either Rapilin or NovoRapid (Figure 1). Block randomization using numbers generated by PROC PLAN SAS software was utilized. The study protocol was approved by the Ethics Committee of Peking University First Hospital and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients prior to study entry. The patients were provided with blood glucose meters and test strips and were instructed in the proper use of the blood glucose meter, including how to perform regular calibrations according to the factory instructions. The patients were required to perform 7-point blood glucose measurements (before breakfast, 2 h after breakfast, before lunch, 2 h after lunch, before dinner, 2 h after dinner, and before bed) any 2 consecutive days prior to all outpatient and telephone visits. Outpatient or telephone consultations were conducted weekly during the first 8 weeks, and then every 2 weeks during weeks 8–12, and every 4 weeks for the last 12–24 weeks. Specimens collected at weeks 0, 12, and 24 were analyzed at a central laboratory. Patients meeting the criteria for serious hyperglycemia after week 12 received insulin glargine at the discretion of the study investigator; otherwise, patients were not permitted to receive insulin formulations other than the study medication.

Patient population

Patients with type 2 diabetes mellitus aged 18–75 years who had glycated hemoglobin (HbA1c) levels of $>7.5\%$ to $\leq 13\%$ (centralized laboratory confirmed), had previously undergone treatment with metformin (≥ 1000 and ≤ 2000 mg) or ≤ 3 oral antidiabetes drugs (OADs, sulfonylureas, nonsulfonylurea insulin secretagogues, and glucosidase inhibitors) for more than 3 months prior to screening, and had a body mass index (BMI) of <40 kg/m^2 were eligible for the study. Although not specifically excluded by the study protocol, patients had not received prior sodium-glucose co-transporter 2 (SGLT2) inhibitors as they were not available in China during the period the study was active[16,17]. Exclusion criteria included insulin treatment in the 6 months prior to screening; thiazolidinedione, human glucagon-like peptide-1 receptor agonist, or dipeptidyl peptidase 4 inhibitor treatment in the 3 months prior to screening, and a history of severe hypo/hyperglycemia. Patients with a known

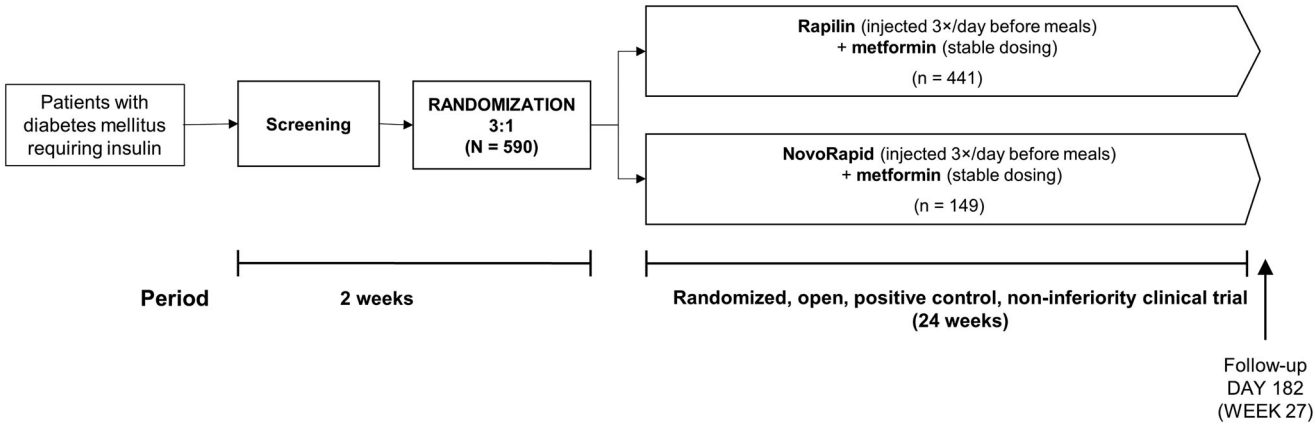

Figure 1. Study design.

hypersensitivity to study drugs; glucocorticoid use in the 2 months prior to screening; alcohol/substance abuse in the 5 years prior to screening; or those who were pregnant, breastfeeding, or at risk of pregnancy were also excluded.

Interventions

Rapilin was supplied as a 3-mL pre-filled pen injector at a concentration of 100 U/mL for subcutaneous injection (batch no. 72130301). NovoRapid was supplied as a 100 U/mL insulin solution for subcutaneous injection in a 3-mL prefilled pen injector (batch nos. PW50009, PW50875, and PW51095). Patient compliance to insulin injections was recorded *via* patient diaries. The initial dose of Rapilin or NovoRapid was 0.3–0.4 U/kg/day, equally divided into three doses administered 5 min before meals (breakfast, lunch, and dinner). After assessing blood glucose values *via* 7-point plasma glucose self-monitoring, insulin dosages were adjusted accordingly (blood glucose fasting, 4.4–6.1 mmol/L, and nonfasting, $<$8.0 mmol/L: dose adjustment, 0 U; blood glucose fasting, $\leq$7.8 mmol/L, and nonfasting, $<$10.0 mmol/L: dose adjustment, +2–4 U; blood glucose fasting, $>$7.8 mmol/L, and nonfasting, $>$10.0 mmol/L: dose adjustment +4–6 U)[18]. The maximum amount added daily was 8 U. Dose adjustments were permitted throughout the study.

All patients received treatment with metformin hydrochloride tablets, Glucophage (Sino-American Shanghai Squibb Pharmaceuticals Co., Ltd; 500 mg/tablet) and discontinued other OADs. After the screening period, all patients continued to receive metformin 1–3 times a day at their previous dosing, except those previously receiving a dose of 1000 mg/day whose dose was increased to 1500 mg/day. During the treatment period, the metformin dose could only be reduced to a minimum of 1000 mg/day following serious gastrointestinal adverse events, and a metformin dose of 1000–2000 mg/day was maintained for all patients. Patients had to withdraw from the study if the metformin dose was lowered to less than 1000 mg/day.

Patients with laboratory-confirmed serious hyperglycemia (fasting plasma glucose [FPG] $>$ 234 mg/dL [13 mmol/L]) occurring after 12 weeks of treatment, who were not diagnosed with a treatable hyperglycemia pathogeny, received 12 U of insulin glargine (Basalin[iii]; Gan & Lee Pharmaceutical Co Ltd) daily, administered subcutaneously at bedtime using a 3-mL prefilled pen injector dispensing a concentration of 100 U/mL, which remained unchanged for the treatment period.

Outcomes assessed

The primary efficacy endpoint was the change from baseline in HbA1c (determined in a blinded central laboratory using Quintiles Laboratories High Pressure Liquid Chromatography) after 24 weeks of treatment. Secondary efficacy endpoints included the change from baseline in 2-hour PPG (fasting blood glucose levels were measured prior to drug administration and consumption of a standard meal; 2 h after the meal, postprandial blood glucose levels were measured) and FPG (fingertip blood glucose determined in a central laboratory using the Johnson & Johnson OneTouch UltraEasy blood glucose meter), and the percentages of patients who achieved HbA1C targets of $<$7.0% and $\leq$6.5% after 24 weeks. Additional outcomes included the total daily insulin dose, body weight, and treatment compliance.

The safety outcomes included the proportion of patients who experienced at least one hypoglycemic episode; the number of patients with treatment-emergent adverse events (AEs) and serious adverse events (SAEs); routine laboratory assessments; the proportion of patients who developed anti-insulin aspart antibodies (determined using sandwich enzyme-linked immunosorbent assay, conducted centrally at Covance laboratories); and the proportion of patients with abnormal electrocardiograms. AEs were defined as any adverse medical event taking place after the patient received study medication and were coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Hypoglycemic events were recorded by patients in their daily log, including all blood glucose values of $\leq$3.9 mmol/L (70 mg/dL) or values of $>$3.9 mmol/L (70 mg/dL) if they were accompanied by hypoglycemia symptoms. Hypoglycemia episodes were categorized based on American Diabetes Association classifications[19,20]. These included severe hypoglycemia (an event that required help from others to effectively administer carbohydrates, glucagon, or other recovery measures); documented symptomatic hypoglycemia (an event accompanied by typical hypoglycemia symptoms and

blood glucose measured at ≤3.9 mmol/L [70 mg/dL]); asymptomatic hypoglycemia (an event not accompanied by typical hypoglycemia symptoms, but with blood glucose measured at ≤3.9 mmol/L [70 mg/dL]); probable symptomatic hypoglycemia (an event with hypoglycemia symptoms, but no blood glucose monitoring value) and relative hypoglycemia (an event when the patient reports typical hypoglycemia symptoms and interprets them as a manifestation of hypoglycemia, but with blood glucose measured at >3.9 mmol/L [70 mg/dL]). There was an additional classification of a mild hypoglycemic event defined as a blood glucose value of <2.8 mmol/L (50 mg/dL) with no symptoms or symptoms that the patient was able to manage by themselves. Only hypoglycemic events meeting the criteria for an SAE (AEs requiring new or prolonged hospitalization, which lead to permanent disability, impact the ability to work, or are life-threatening) were recorded as AEs.

Statistical analyses

The sample size was calculated to test the noninferiority of Rapilin to NovoRapid with respect to the primary efficacy endpoint of HbA1c change from baseline to 24 weeks, with a noninferiority upper margin of 0.4% (standard deviation of 1.25%; 2.5% significance level; one-sided t-test)[21]. Assuming a 20% dropout rate and considering regulatory requirements for at least 300 patients in the Rapilin arm, a total of 592 patients would provide 85% power to demonstrate noninferiority of Rapilin to NovoRapid with a 3:1 randomization ratio.

Efficacy outcomes were analyzed in the full analysis set (FAS) population, which included all randomized patients. The primary efficacy endpoint (change in HbA1c from baseline to 24 weeks) was examined using an analysis of covariance (ANCOVA) model with baseline HbA1c as the continuous fixed covariate and treatment group and center as fixed-effect factors. The least squares (LS) mean change in HbA1c from baseline to 24 weeks for each treatment group was estimated, as well as the between-group difference and the 95% confidence interval (CI) for the adjusted mean. Missing data were imputed using the last observation carried forward (LOCF) estimation. Post-hoc, the ANCOVA model was adjusted to include biological sex and disease duration as additional fixed-effect factors. Changes in 2-hour PPG and FPG were analyzed using a similar LOCF imputation method and similar ANCOVA models. The proportions of patients meeting HbA1c targets (<7.0% and ≤6.5%) were analyzed using a logistic regression model, where the treatment group and center were independent variables, and baseline HbA1c was a dependent variable. A p value <.05 was considered statistically significant.

Prespecified subgroup analysis included all patients who received insulin glargine from 12 weeks. Change from baseline in HbA1c, 2-hour PPG and FPG were analyzed using LOCF imputation and similar ANCOVA models as utilized for the pre-specified FAS analysis. Additionally, a post-hoc analysis of change from baseline in HbA1c and 2-hour PPG after 24 weeks in subgroups of patients grouped based on their baseline HbA1c category (≥7.5% – <9%, ≥9% – <11%, ≥11%) was conducted using LOCF imputation and student's t-test. Differences were calculated between baseline and 24 weeks, and between treatment groups, but not between subgroups.

Safety was evaluated using the safety population, which was defined as the FAS population excluding patients who never received treatment. Treatment duration was defined as the time from a first randomized dose of study medication to the last randomized dose. The differences in the number of hypoglycemic events between the two treatment groups were analyzed using a chi-squared test and Fisher's exact test. Insulin aspart antibodies were assessed in the FAS population for 12 weeks using a grouped t-test or Wilcoxon rank-sum test for inter-group comparisons, and a paired t-test for intra-group comparisons; patients who received insulin glargine were excluded from the analysis following insulin glargine treatment initiation. Analyses were performed using SAS version 9.1.3 or higher (SAS Institute, Inc., Cary, NC).

Ethics approval

Approval was obtained from the ethics committee of Peking University First Hospital. The procedures used in this study adhere to the tenets of the Declaration of Helsinki. All volunteers provided written informed consent to participate in the study.

Results

Trial participants and baseline characteristics

In total, 590 patients from 21 centers were enrolled and randomized to receive Rapilin ($n = 441$) and NovoRapid ($n = 149$) and included in the FAS population. Of these patients, 588 received randomized treatment (439 in the Rapilin group and 149 in the NovoRapid group) and were included in the safety analysis; 399 patients (90.48%) and 144 patients (96.64%) completed the trial for 24 weeks in the Rapilin and NovoRapid groups, respectively (Figure 2). The most common reasons for withdrawal were patient decision to discontinue in both treatment groups and loss of follow-up in the Rapilin group (Figure 2). The mean treatment duration was comparable between groups (mean ± standard deviation: 161.99 ± 35.03 days for Rapilin and 164.93 ± 25.92 days for NovoRapid). Overall drug usage rates of 80–120% (considered compliant) were reported by 417 (99.3%) patients in the Rapilin group and 146 (100%) patients in the NovoRapid group.

Demographics and baseline characteristics, including disease duration and the treatment duration, were similar between treatment groups (Table 2). All randomized patients had a diagnosis of type 2 diabetes mellitus, with a mean age of 56 years, mean BMI of 25.7 kg/m^2, mean disease duration of 8.4 years, and mean HbA1c value of 9.5%. There were relatively more males in the Rapilin group compared with the NovoRapid group (56.2% versus 44.3%, respectively, Table 2).

Efficacy

After 24 weeks, the mean change in HbA1c from baseline was reported as −2.20% for the Rapilin treatment group and

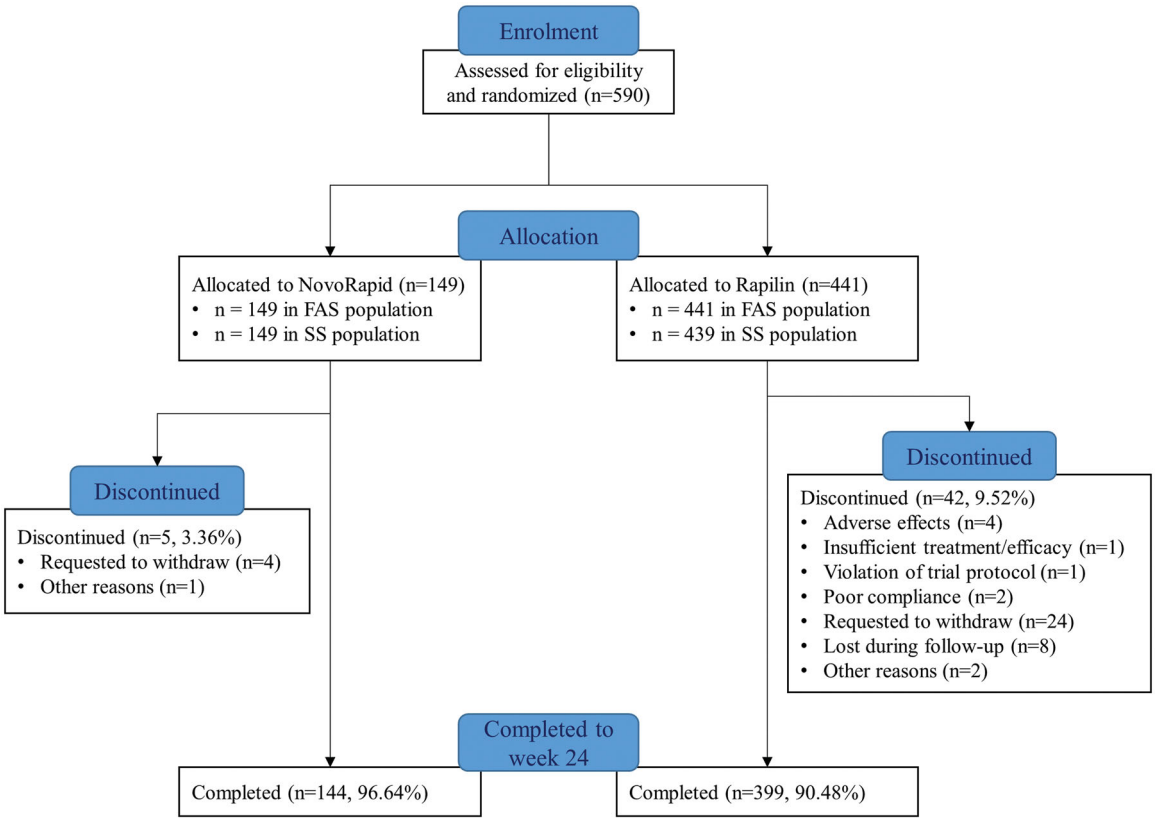

Figure 2. Patient enrolment. Abbreviations. FAS: Full analysis set; SS: Safety set.

Table 2. Demographic and baseline characteristics of patients (FAS population).

	Rapilin ($n = 441$)	NovoRapid ($n = 149$)
Type 2 diabetes mellitus (n [%])	441 (100)	149 (100)
Male gender (n [%])	248 (56.2)	66 (44.3)*
Age, years	56.31 ± 9.65	54.90 ± 10.39
BMI, kg/m^2	25.71 ± 3.31	25.66 ± 3.82
Diabetes duration, years	8.66 ± 5.64	7.74 ± 4.89
HbA1c, %	9.52 ± 1.35	9.58 ± 1.37
≥ 7.5% – < 9% (n [%])	187 (42.4)	59 (39.6)
≥ 9% – < 11% (n [%])	179 (40.6)	60 (40.3)
≥ 11% (n [%])	75 (17.0)	30 (20.1)
2-h PPG, mmol/L	17.53 ± 4.21	17.82 ± 4.09
FPG, mmol/L	10.94 ± 3.35	10.87 ± 3.25

Abbreviations. BMI: body mass index; 2-h PPG: 2-hour postprandial plasma glucose; FAS: Full Analysis Set; FPG: fasting plasma glucose; HbA1c: glycated hemoglobin; SD: Standard Deviation. Data presented as Mean ± SD.
*$p < .05$ versus comparison between groups.

Table 3. Comparison of HbA1c, 2-hour PPG, and FPG at 24 weeks between the two treatment groups (mean ± standard deviation).

	Rapilin ($n = 441$)	NovoRapid ($n = 149$)
HbA1c (%)		
Absolute	7.31 ± 1.23*	7.26 ± 1.12*
Change from baseline	−2.20% ± 1.57%	−2.32% ± 1.64%
2-h PPG (mmol/L)		
Absolute	11.41 ± 4.15*	11.53 ± 4.46*
Change from baseline	−6.14 ± 5.32	−6.29 ± 5.21
FPG (mmol/L)		
Absolute	8.92 ± 2.60*	9.15 ± 2.62*
Change from baseline	−2.02 ± 3.56	−1.70 ± 3.06

Abbreviations. 2-h PPG: 2-hour postprandial plasma glucose; FPG: fasting plasma glucose; HbA1c: glycated hemoglobin.
*$p < .05$ versus pre-therapy in the same group.

−2.32% for the NovoRapid group (Table 3, Figure 3A). The estimated treatment difference (ETD) between LS mean changes in HbA1c from baseline after 24 weeks was 0.04% (95% CI: −0.17, 0.26), which met the noninferiority criteria for Rapilin relative to NovoRapid (Table 4). No interactions between centers and treatment groups were detected ($p = .7829$), and similar results were calculated when the model was adjusted post-hoc to include biological sex and disease duration (ETD [95% CI]: 0.05% [–0.17, 0.26]). Between treatment differences were consistent across baseline HbA1c categories when analyzed post-hoc (Figure 4, $p > .1$ between treatment groups across HbA1c categories). Comparable proportions of patients achieved target HbA1c values of <7.0% (Rapilin: 52.6%; NovoRapid: 51.0%) and ≤6.5% (Rapilin: 34.2%; NovoRapid: 30.9%) at 24 weeks.

Both treatment groups had comparable reductions in FPG (–2.02 mmol/L following Rapilin; −1.70 mmol/L following NovoRapid; Table 3, Figure 3B), with no significant differences between groups ($p = .2906$). Similarly, the mean observed 2-hour PPG change from baseline to week 24 was comparable between treatment groups with no statistically significant differences (–6.14 mmol/L following Rapilin; −6.29 mmol/L following NovoRapid; Table 3, Figure 3C; $p = .3527$). Post-hoc analyses demonstrated similar trends across baseline HbA1c categories (Figure 4, $p > .1$ between treatment groups across HbA1c categories).

The mean body weight change from baseline to week 24 was comparable between the two groups (Rapilin: 1.72 ± 3.10 kg versus NovoRapid: 1.87 ± 2.77 kg), with no statistically significant differences detected ($p = .5918$). No clinically relevant differences in dosing were observed between treatment groups. Initial mean insulin doses were 0.32 ± 0.08 and 0.33 ± 0.07 U/kg/day in the Rapilin and NovoRapid

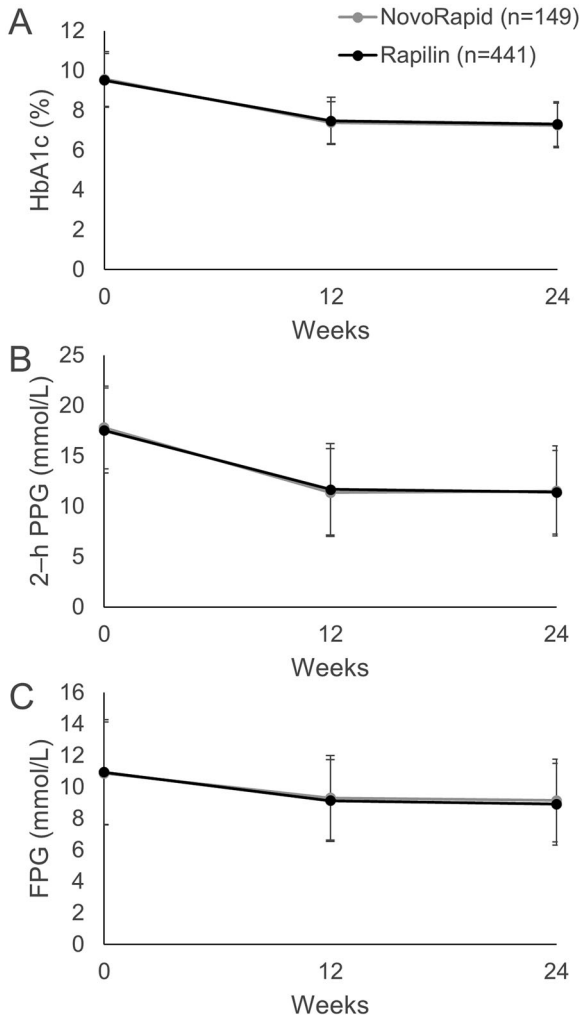

Figure 3. Mean and standard deviation values of HbA1c (A), 2-h PPG (B), and FPG (C) at weeks 0, 12, and 24. Abbreviations. 2-h PPG: 2-hour postprandial plasma glucose; FPG: fasting plasma glucose; HbA1c: glycated hemoglobin.

Table 4. Results of the analysis of covariance of changes in HbA1c from baseline to the end of week 24 (LS mean and 95% CI).

		Rapilin ($n = 441$)	NovoRapid ($n = 149$)	Rapilin-NovoRapid
HbA1c (%)	LS mean	−2.16	−2.20	0.04
	95% CIL	−2.29	−2.40	−0.17
	95% CIU	−2.03	−2.00	0.26

Abbreviations. CIL: confidence interval lower; CIU: confidence interval upper; HbA1c: glycated hemoglobin; LS: least-squares.

groups, respectively. Following 24 weeks of treatment, mean doses were 0.55 ± 0.26 U/kg/day in the Rapilin group and 0.56 ± 0.26 U/kg/day in the NovoRapid group, with an ETD of 0.01 U/kg/day (95% CI: −0.01, 0.04)

Insulin glargine use following week 12

After 12 weeks of treatment, 12 patients in the Rapilin group and five in the NovoRapid group experienced severe fasting hyperglycemia (FPG >13 mmol/L) and initiated treatment with insulin glargine. In this subpopulation, after 24 weeks of study medication, the mean ± standard deviation change in HbA1c level from baseline was −2.12% ± 1.56% and

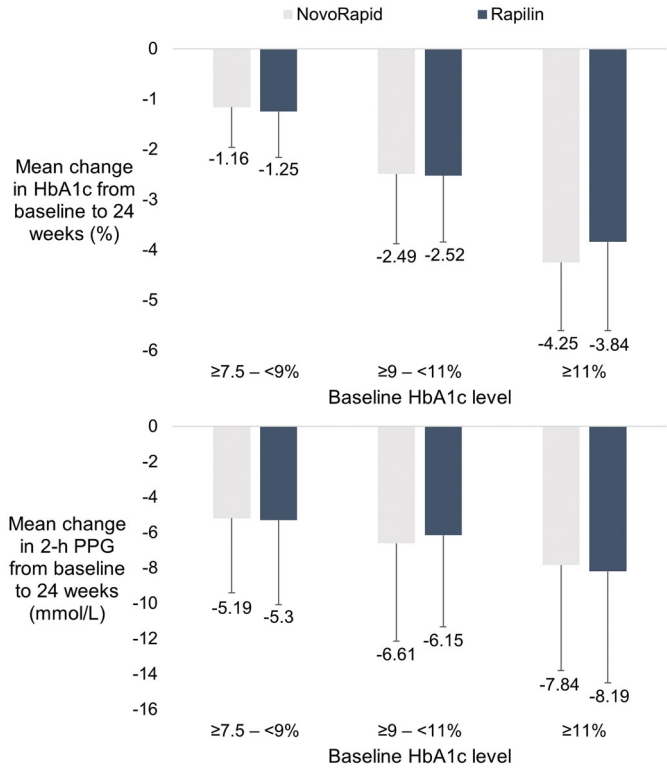

Figure 4. Post-hoc subgroup analysis outcomes (change in HbA1c and 2-h PPG at baseline HbA1c values ≥7.5–<9%, ≥9–<11%, and ≥11%). Abbreviations. 2-h PPG: 2-hour postprandial plasma glucose; HbA1c: glycated hemoglobin.

−3.44% ± 2.48% ($p = .1996$); FPG was −2.76 ± 4.20 and −5.71 ± 3.51 mmol/L ($p = .1890$); and 2-hour PPG was −8.31 ± 6.52 mmol/L and −12.02 ± 3.78 mmol/L ($p = .2568$) in the Rapilin and NovoRapid groups, respectively for all three clinical parameters studied.

Safety endpoints

During the 24-week treatment period, just over half of the patients experienced a hypoglycemic event, with comparable rates observed between treatment groups (Rapilin: 59.0%, NovoRapid: 59.1%; $p = .9893$; Table 5). Numerically fewer patients experienced a nocturnal hypoglycemic event in the Rapilin group (5.01%) compared to the NovoRapid group (8.05%), however, this difference was not statistically significant ($p = .1692$; Table 5). Symptomatic hypoglycemia was experienced by 37.8% and 44.3% of patients in the Rapilin and NovoRapid groups ($p = .1619$, Table 5), respectively; 25.3% (Rapilin) and 22.2% (NovoRapid) of the patients experienced nonsymptomatic hypoglycemia ($p = .4416$, Table 5). One patient (0.23%) in the Rapilin group experienced severe hypoglycemia caused by a lack of carbohydrates. No severe hypoglycemia was observed in the NovoRapid group.

Both Rapilin and NovoRapid were well tolerated, with comparable proportions of patients reporting AEs (Rapilin: 43.7%, NovoRapid: 41.6%; $p = .6509$; Table 5). The nonhypoglycemia treatment-associated AEs in the Rapilin group comprised one case of mild palpebral edema and one of mild drug hypersensitivity. The cases in the NovoRapid group comprised one case each of mild palpebral edema, mild

Table 5. Reported adverse events.

	Rapilin ($n = 439$)	NovoRapid ($n = 149$)	p value
Hypoglycemic event, % (n)	59.0 (259)	59.1 (88)	.9893
Nocturnal hypoglycemic event, % (n)	5.0 (22)	8.1 (12)	.1692
Daytime hypoglycemic event, % (n)	56.7 (249)	55.7 (83)	.8290
Symptomatic hypoglycemic event, % (n)	37.8 (166)	44.3 (66)	.1619
Nonsymptomatic hyperglycemic event, % (n)	25.3 (111)	22.2 (33)	.4416
AEs, * % (n)	43.7 (192)	41.6 (62)	.6509
Study drug-associated AEs, % (n)	0.68 (3)	1.34 (2)	.6050
Serious AEs, % (n)	3.87 (17)	0.67 (1)	.0543

Abbreviation. AE: adverse event; *Only cases of hyperglycemia classified as severe were recorded as an AE.

peripheral edema, and mild subcutaneous induration. Cases of SAEs were comparable between the two groups (Table 5). In the Rapilin group, 17 (3.87%) patients reported SAEs, with the previously noted case of severe hypoglycemia considered study drug-related. There was one (0.67%) SAE in the NovoRapid group, but this was not considered to be related to the study drug (Table 5). After the 24-week treatment period, no clinically significant differences in vital signs, laboratory assessments, or electrocardiograms were observed between the treatment groups.

The rate of positive insulin aspart-specific antibodies was comparable following Rapilin and NovoRapid treatment to 24 weeks, with no statistically significant difference between groups (odds ratio [95% CI]: 0.7281 [0.2751, 1.9273]; $p > .05$). The positive rate of insulin aspart-specific antibodies was 2.51% (Rapilin) and 3.36% (NovoRapid) at baseline, 2.49% (Rapilin), and 2.82% (NovoRapid) at week 12, and 2.96% (Rapilin), and 4.70% (NovoRapid) at week 24.

Discussion

Mealtime insulin secretion controls PPG and HbA1c[22,23], ameliorating risk factors for multiple cardiovascular complications[24]. Efficient use of fast-acting insulin is therefore associated with increased life expectancy and is highly cost-effective[25]. The reference insulin aspart, NovoRapid, has proven efficacy for effective blood glucose control with an acceptable safety profile[8]. It can be administered immediately before mealtimes, leading to demonstrated improvements in quality of life, and has been successfully used both globally and in China since its introduction in 1999[26–28]. In this study, the efficacy and safety of two insulin aspart formulations, Rapilin and NovoRapid, both used in combination with metformin, were compared for the treatment of patients with type 2 diabetes mellitus.

Biosimilars or domestic insulins have the potential to reduce treatment costs by 20%, which have been rising steadily for patients with diabetes mellitus over the last decades[3,29]. This reduction in costs is anticipated to improve patient access to insulin analogs in particular, as these are still prohibitively expensive compared to recombinant human insulin for many patients, despite documented clinical benefits[30]. The first biosimilar insulin analog approved in Europe was a biosimilar of long-acting insulin glargine Abasaglar[iv] in 2014[29]. Since then, fast-acting insulin biosimilars SAR342434 (insulin lispro, Sanofi-Aventis) and SAR341402 (insulin aspart, Sanofi-Aventis) have also gained regulatory approval in Europe and the USA (SAR342434 only)[31–33]. In countries outside of the EU and USA, such as India and China, some biosimilar and domestic insulin analogs were approved for use before 2014. Additionally, there is some evidence that biosimilar insulin products are associated with reduced drug acquisition costs, particularly for fast-acting insulins[30].

In our study, Rapilin was demonstrated to be noninferior to commercially available NovoRapid, when used in combination with metformin to treat patients with type 2 diabetes, as measured by change from baseline in HbAlc levels over 24 weeks of treatment (Figure 3A, Table 4). Improvement in glycemic control was matched in both treatment groups, with comparable insulin dosing and changes in body weight (Figure 3, Table 3). The proportions of patients achieving HbA1c targets of $<7.0\%$ and $\leq 6.5\%$ were also comparable between the Rapilin and NovoRapid groups, and numerically similar to those reported by other studies investigating the use of insulin aspart[8,34].

Noninferiority of Rapilin to NovoRapid was determined using a pre-specified HbA1c margin of 0.4% based on FDA guidance provided at the time of the study[21]. Recent studies have used the more stringent of the FDA recommended margins (0.3%) to establish noninferiority[29,35,32], although 0.4% has also been reported[36]. However, as the confidence intervals of the treatment difference observed in this study (0.04% [95% CI: −0.17, 0.26]) were within ±0.3% of 0, thereby falling within the 0.3% margin, noninferiority would have been demonstrated irrespective of the FDA recommended margin used.

Baseline HbA1c levels were comparable between treatment groups (Table 2), and slightly higher than in other studies of insulin aspart published to date[8,34]. This was primarily due to a higher maximum cut-off for HbA1c level at enrollment compared to similar studies, with ∼20% of patients reporting a baseline HbA1c level over 11%. Nationally, glucose control remains poor in China, with less than half of patients with type 2 diabetes achieving adequate control (defined as HbA1c 7%) and widespread treatment inertia[37], which was reflected in the recruited study population. This may also explain the slightly higher mean reductions in HbA1c reported in this study compared to similar trials[8,34]. A post-hoc subgroup analysis demonstrated that HbA1c reductions were substantially higher in patients with high baseline HbA1c levels, as would be expected (Figure 4). There were no significant differences in efficacy between treatment groups in any of the HbA1c categories. Prandial insulin in combination with metformin, even in the absence of basal insulin treatment, showed promising efficacy with a $> 2\%$ decrease in HbA1c levels and decreased

fasting blood glucose levels (Figure 3, Table 3). The results of this study provide evidence supporting the use of insulin for the treatment of patients with type 2 diabetes mellitus.

The majority of studies investigating insulin aspart involve a combined treatment approach with basal insulin. Current evidence supporting the use of insulin aspart as insulin therapy, in combination with metformin, for the treatment of type 2 diabetes mellitus is limited. A previous randomized, open-label, cross-over study recruiting 30 patients with type 2 diabetes, compared mealtime insulin aspart and human insulin in combination with metformin. Patients were assigned to a treatment group and switched to the alternate insulin following 90 days (12.9 weeks) of treatment. The study reported significantly decreased HbA1c and blood glucose area under the curve with insulin aspart compared to human insulin, with no significant change in HbA1c level detected in the human insulin treatment group[11]. Our trial found comparably significant reductions in HbA1c and FPG changes from baseline for both Rapilin and NovoRapid treatment groups, supporting the findings of the previous study.

The most common adverse event associated with insulin therapy, including insulin aspart, is hypoglycemia[6,15]. Hypoglycemia episodes were observed at comparable rates in the Rapilin and NovoRapid groups (Table 5). Unlike most previous studies of insulin aspart[8,34,38], this trial did not mandate basal insulin as a background medication, and only a small proportion of patients received basal insulin (insulin glargine) from week 12 of the study. This may be the reason for the lower overall rates of hypoglycemia reported in our study compared to most studies investigating insulin aspart[8,34]. A large-scale noninterventional study reported reductions in the rates of hypoglycemic events in patients who switched from other insulin regimens to receiving insulin aspart[12]. It may also have contributed to good compliance rates throughout the study, with the majority (>99%) of patients reporting drug use compliance of 80–120%. Subgroup analyses did not demonstrate differences between Rapilin and NovoRapid efficacy when used in combination with insulin glargine, but patient numbers in this sub-population were low.

Both Rapilin and NovoRapid were well tolerated, with the majority of adverse events classified as mild over 24 weeks of therapy (Table 5). There were no significant differences between the safety profile of Rapilin and the AE profile previously reported for NovoRapid in patients with type 2 diabetes mellitus[6,15]. Common clinical adverse events related to the study drugs were observed in less than 5% of patients (Table 5), including palpebral edema, lower extremity edema, lumps in abdominal injection sites, and drug allergies. These are attributed to the permeability of blood vessels to insulin, the effects of insulin on subcutaneous fat, and patient characteristics[39]. These findings support the results of a previous study comparing insulin aspart and human insulin in combination with metformin, which reported only mild hypoglycemic events with no difference between treatment groups[11].

Excessive production of antibodies against insulin affects its function, resulting in poor glycemic control, which is a major safety concern for insulin preparations[40]. Previous studies of insulin aspart have confirmed that intracorporeal insulin antibodies are not significantly increased relative to those induced by human insulin[41,42]. In this study, the positive rate of insulin-specific antibodies was comparable in the Rapilin and NovoRapid treatment groups.

One limitation of this study is that despite the original objective to recruit both patients with type 1 and type 2 diabetes mellitus, no patients with type 1 diabetes mellitus could be included as these patients need basal-bolus therapy[3]. Therefore, it was not feasible to recruit patients with type 1 diabetes who had not received insulin in the previous 6 months. An additional potential limitation of the study was the open-label design. To minimize the potential bias that this may have caused, the study investigated objective parameters as the primary efficacy endpoint and laboratory staff were blinded to treatment allocation. The 3:1 randomization ratio may be considered a limitation, but the reasoning behind this ratio was pragmatic and equivalence was still demonstrated. There was also a small, but statistically significant, imbalance in the gender ratio between treatment groups following randomization. However, the differences between treatment groups remained below the threshold for noninferiority when the covariance model was adjusted to include gender post-hoc, suggesting that imbalance did not have a substantial impact on the study results.

Conclusions

This multicenter, randomized, active-controlled, phase III confirmatory study, demonstrated that, in patients with type 2 diabetes mellitus, Rapilin is non-inferior compared to the reference insulin aspart formulation NovoRapid in terms of glycemic control, with similar safety and immunogenicity profiles.

Notes

i. Rapilin is a registered trademark of Gan & Lee Pharmaceuticals Co Ltd, Beijing, China.
ii. NovoRapid is a registered trademark of Novo Nordisk, Bagsvaerd, Denmark.
iii. Basalin is a registered trademark of Gan & Lee Pharmaceuticals Co Ltd, Beijing, China.
iv. Abasaglar is a registered trademark of Eli Lilly and Boehringer Ingelheim,

Transparency

Declaration of funding

This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of financial/other relationships

Damei Wang is an employee of Gan & Lee Pharmaceuticals Co Ltd. Other authors declare no financial relationships. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

All authors contributed to the conception and design, analysis and interpretation of the data, and revising paper critically for intellectual content. Jun Yao and Xiaohui Guo also contributed to the drafting of the paper. All authors gave their final approval of the version to be published and agree to be accountable for all aspects of the work.

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Data availability statement

The data that support the findings of this study are openly available at http://www.medresman.org.cn.

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