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ORIGINAL RESEARCH

Immune Persistence and Safety After SARS-CoV-2 BNT162b1 mRNA Vaccination in Chinese Adults: A Randomized, Placebo-Controlled, Double-Blind Phase 1 Trial

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ABSTRACT

Introduction: BNT162b1 is a lipid nanoparticle-formulated, nucleoside-modified mRNA SARS-CoV-2 vaccine. Here, we report safety and immune persistence data following a primary two-dose vaccination schedule administered 21 days apart.

Methods: Immune persistence was determined at month 3 in 72 younger participants (aged 18–55 years) and at month 6 in 70 younger and 69 older participants (aged 65–85 years).

Results: In younger participants, neutralizing antibody (nAb) geometric mean titers (GMTs) for the 10 and 30 μg dose levels declined from 233 and 254 (21 days after dose 2) to 55 and 87 at month 3, respectively, and to 16 and 27 at month 6, respectively. In older participants, nAb GMTs declined from 80 and 160 (21 days after dose 2) to 10 and 21 at month 6. Overall, higher antibody titers were observed in younger participants, and the 30 μg dose induced higher levels of nAb, which declined more slowly by

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month 6. No serious adverse events were reported in the vaccine group.
Conclusion: This study showed BNT162b1 maintains a favorable safety profile in younger and older participants in the 6 months after vaccination. This study further extends our understanding of immune persistence and the safety of the BNT162b1 vaccine as a candidate vaccine in the BioNTech pipeline.
Trial Registration Number: NCT04523571, registered August 21, 2020.

Keywords: SARS-CoV-2; COVID; mRNA vaccine; Immune persistence

Key Summary Points

mRNA vaccine platforms are crucial in reducing SARS-CoV-2 transmission and improving disease prognosis.

BNT162b1 is a lipid-formulated nucleoside-modified mRNA SARS-CoV-2 vaccine formulation, generated by BioNTech in collaboration with Pfizer and Fosun Pharma.

This brief report described immune persistence data at 3 and 6 months in 144 Chinese adults who received two doses of BNT162b1 vaccine 21 days apart.

This study showed BNT162b1 maintained a favorable safety profile in younger and older participants in the 6 months after vaccination.

INTRODUCTION

SARS-CoV-2, the causative agent of COVID-19, has produced > 360 million confirmed cases and 5.6 million deaths globally as of January 27, 2022 [1]. SARS-CoV-2 vaccine development is critical for the prevention of infection and disease. Vaccine platforms based on messenger RNA (mRNA) are a new development in vaccine technology; they enable rapid, targeted antigen design, accelerating the development of potential vaccine candidates [2, 3].

BioNTech, in collaboration with Pfizer and Fosun Pharma, has launched an extensive vaccine development program involving multiple clinical trials in Germany (phase 1/2; NCT04380701), the USA (phase 1/2/3; NCT04368728) and China (phase 1; ChiCTR2000034825; NCT04523571) [4–7]. Two vaccine candidates, BNT162b1 and BNT162b2, were selected for further investigation. BNT162b1 and BNT162b2 are lipid nanoparticle-formulated, pharmacologically optimized [5, 6, 8, 9], nucleoside-modified mRNA [10] vaccine candidates targeting SARS-CoV-2. BNT162b1 encodes a trimerized, secreted SARS-CoV-2 receptor binding domain (RBD) [11], whereas BNT162b2 encodes the full-length, membrane-anchored spike protein, stabilized in the prefusion conformation.

In a China-based phase 1 study [4], it was shown that BNT162b1 had an acceptable safety and tolerability profile, and a robust humoral and T-cell response, with SARS-CoV-2 neutralizing immunoglobulin G (IgG) titers (21 days after dose 2) up to 2.1-fold higher than in those who had recovered from a natural infection. The results were similar to those observed in the initial clinical trial in Germany [6], which showed that two doses of BNT162b1 elicited robust, non-dose–dependent T-cell responses and RBD-binding IgG concentrations that were up to 3.5-fold higher than in a cohort who had recovered from a natural SARS-CoV-2 infection. In parallel, a phase 1/2 clinical trial was conducted in the US [5], which showed that two doses of 10–30 μg BNT162b1 produced mild-to-moderate, transient, dose-dependent reactions and yielded dose-dependent RBD-binding IgG concentrations and SARS-CoV-2 neutralizing titers, increasing after a second dose.

To determine which of the two vaccine candidates, BNT162b1 or BNT162b2, was more promising, the safety and immunogenicity of BNT162b1 and BNT162b2 were compared; BNT162b2 was found to have milder systemic reactogenicity than BNT162b1, with a humoral and cellular immune response that was broadly similar to that of BNT162b1 [7, 12]. These more favorable safety data have prompted the

decision to advance BNT162b2 to the phase 2/3 trial [13], which has subsequently led to its global roll out.

To gain a better understanding of the long-term safety and efficacy of BNT162b1, here we report safety and immune-persistence data at month 3 and month 6 in participants who received two doses of the SARS-CoV-2 BNT162b1 vaccine.

METHODS

Study Design

We previously reported preliminary safety and immunogenicity of a SARS-CoV-2 mRNA vaccine candidate, BNT162b1, in healthy Chinese adults aged 18–55 years or 65–85 years in a phase 1, randomized, placebo-controlled, observed-blind study [4]. Here, we report the immune persistence and safety of BNT162b1 vaccine in those participants over a 6-month follow-up period (NCT04523571, ChiCTR2000034825). Only those participants who had received two doses of the active treatment or placebo were included in the immune persistence analysis.

Compliance with Ethics Guidelines

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol was approved by Chinese NMPA and the institutional review board of the Jiangsu Provincial Center of Disease Control and Prevention. Informed consent was obtained from all individual participants included in the study.

Outcomes

Geometric mean titer, seroconversion rate and geometric mean fold increase of virus-neutralizing antibody, anti-S1 IgG and anti-RBD IgG were used to assess antibody persistence. Serious adverse events were collected during the follow-up period and graded according to the guidelines set by the China National Medical Products Administration [14] and the US Food and Drug Administration [15] and categorized by investigators as possibly, probably or definitely vaccine-related.

Immune Persistence Assessment

To assess antibody persistence, sera were collected 3 (for younger adults only) and 6 (for younger and older adults) months after the first vaccination to determine total anti-SARS-CoV-2 neutralizing antibodies, anti-S1 IgG and anti-RBD IgG antibody titers by ELISA. A cytopathic effect-based microneutralization assay was used to determine SARS-CoV-2–specific neutralizing antibody titers [4]. Seroconversion is defined as an increase by a factor of 4 or more in antibody titer over baseline, or the lower limit value if the baseline titer is below the limit of detection. Antibody titers were compared by calculating the geometric mean fold increase (GMFI). More detailed information can be found in the previous published phase 1 study [4].

RESULTS

Participant disposition and baseline demographics have been previously reported [4]. In brief, between July 18 and August 14, 2020, 144 eligible participants (72 participants aged 18–55 and 72 aged 65–85 years) were randomized 1:1:1 to receive two doses (10 or 30 μg) of the BNT162b1 vaccine or placebo, 21 days apart. Two participants in the older group (one in each of the 10 and 30 μg dose groups) withdrew before receiving the second dose because of adverse events [4]; additionally, one older and two younger participants in the placebo group were lost to follow-up before the 6-month time point. Sixty-nine patients in the older group and 70 patients in the younger group were therefore eligible for full analysis.

Preliminary safety and tolerability data through day 28 after the second vaccination have been previously reported [4]. No

additional serious adverse events were reported in the vaccine groups by the 6 month follow-up. One serious adverse event (a thyrolingual cyst 152 days after the second dose of placebo, which resulted in hospitalization and resolved within 12 days) was reported in a 42-year-old woman in the placebo group during the follow-up period.

The highest neutralizing antibody (nAb), anti-S1 IgG, and anti-RBD IgG antibody geometric mean titers (GMTs) were recorded on day 43 (21 days after the second dose) in both dose groups (10 and 30 μg), as previously reported [4]. Antibody titers at month 3 (day 85) and month 6 (day 184) after the first dose are shown in Fig. 1 and Table 1. As compared with the peak titer on day 43, GMTs of nAb for the 10 and 30 μg doses in younger participants declined from 233 (95% confidence interval [CI] 151–359) and 254 (95% CI 185–349) to 55 (95% CI 38–79) and 87 (95% CI 64–118) at month 3 and to 16 (95% CI 11–24) and 27 (95% CI 20–37) at month 6, respectively. In older participants, GMTs of nAb at month 6 declined from 80 (95% CI 49–130) and 160 (95% CI 97–265) to 10 (95% CI 7–14) and 21 (95% CI 13–32), respectively. Similar declining trends were also found in GMTs and the geometric mean fold increase (GMFI) of binding anti-S1 IgG and anti-RBD IgG for the 10 and 30 μg doses in both the younger and older adult groups.

The BNT162b1 vaccine elicited antibody responses in a dose-dependent manner, with higher antibody titers observed in those receiving the 30 μg dose (vs. the 10 μg dose). After mounting a peak response, the titers of all three types of antibody gradually declined in both age groups through month 6 (Fig. 1). However, those induced by the 30 μg dose declined more slowly over this period.

Seroconversion rates (SCRs) are shown in Table 1. In younger participants, SCRs of nAb declined from 100 to 88% for the 10 μg dose level and remained 100% for the 30 μg dose level at month 3. SCRs declined further to 58% (10 μg) and 83% (30 μg) at month 6. In older adults, SCRs of nAb at month 6 were 30% (10 μg) and 61% (30 μg) at month 6. The anti-S1 IgG SCR remained 100% for both dose levels in both younger (at months 3 and 6) and older (at month 6) participants. Anti-RBD IgG SCRs in younger participants were 100% for 10 and 30 μg doses at months 3 and 6. In older participants, anti-RBD IgG SCRs at month 6 remained 100% for the 10 μg dose but declined from 100 to 96% for the 30 μg dose.

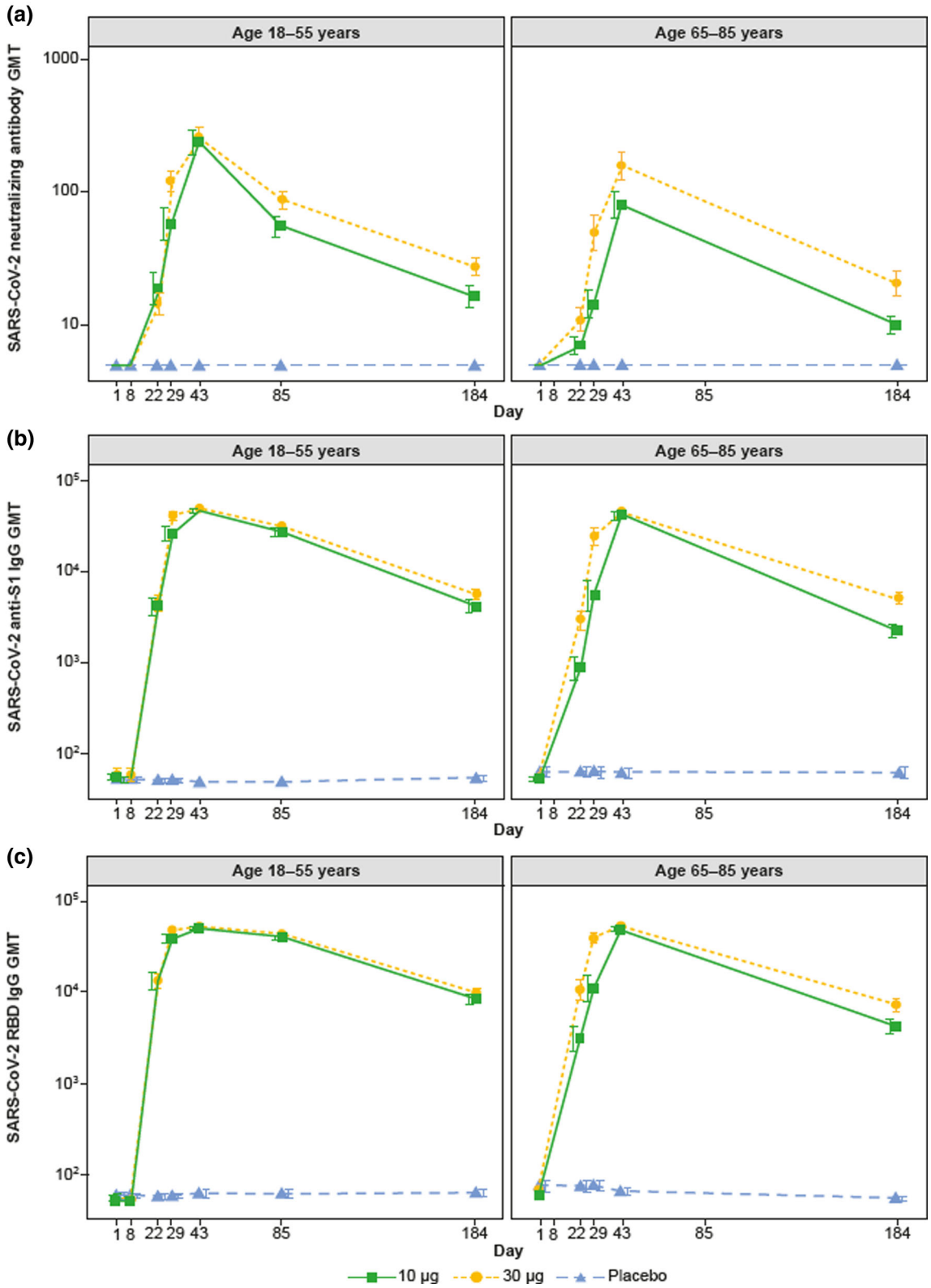
The significant BNT162b1-induced Sp1-reactive T-cell responses on day 29 and day 43 have been reported previously [4]. Similar to GMTs of nAb and binding IgGs, at month 6, geometric mean IFN-γ^+ spot counts for the 10 and 30 μg doses in younger participants declined from 36 (95% CI 21– 60) and 51 (95% CI 30–86) to 15 (95% CI 8–29) and 18 (95% CI 12–28) per 10^5 peripheral blood mononuclear cells (PBMCs), respectively, compared to 2 (95% CI 1–3) per 10^5 PBMCs for the placebo controls.

DISCUSSION

Initial clinical trials examining the safety, tolerability, and immunogenicity of both BNT162b1 and BNT162b2 conducted in the US, Germany and China [4–7, 12] showed that both candidate vaccines demonstrated an acceptable level of immunogenicity.

Twenty-one to 28 days after administration of a second vaccine dose, systemic events after administration of BNT162b1 were more severe than those following vaccination with BNT162b2; the incidence of fever in participants in the younger and older groups after the second dose of 30 μg of BNT162b1 was 75% and 33%, respectively, compared to 17% and 8% in the BNT162b2 group [7]. BNT162b2 has been shown to maintain a favorable safety profile up to 6 months post full vaccination [16].

SARS-CoV-2 antibodies were induced by BNT162b1 in a dose-dependent manner in the 18–55 years and 65–85 years age groups and only marginal differences were observed in nAb GMT across both doses, peaking at 21 days after the primary two-dose vaccination schedule, which is in line with reporting from trials conducted in the US and Germany [5–7, 12]. Moreover, the two doses showed different extents of waning immunity, with the 30 μg vaccine eliciting higher antibody titers, which declined more slowly than the 10 μg dose. The


(a)
Age 18–55 years
Age 65–85 years
SARS-CoV-2 neutralizing antibody GMT
1000
100
10
1 8 22 29 43 85 184
Day
(b)
Age 18–55 years
Age 65–85 years
SARS-CoV-2 anti-S1 IgG GMT
10^5
10^4
10^3
10^2
1 8 22 29 43 85 184
Day
(c)
Age 18–55 years
Age 65–85 years
SARS-CoV-2 RBD IgG GMT
10^5
10^4
10^3
10^2
1 8 22 29 43 85 184
Day
10 µg
30 µg
Placebo

◀**Fig. 1** Longitudinal geometric mean titer of virus-neutralizing antibody, anti-S1 IgG and anti-RBD IgG in healthy participants over 6 months. **A** GMT of neutralizing SARS-CoV-2 antibodies. **B** GMT of anti-S1 antibodies. **C** GMT of anti-RBD antibodies. Participants received two doses of BNT162b1 (10 or 30 μg) or placebo (saline) on days 1 and 22. Blood samples were not collected from older participants (aged 65–85 years) at day 8 and 3 months after dose 1. The error bar was standard error. *anti-RBD IgG* antibody to receptor binding domain, *anti-S1 IgG* antibody to S1 protein, *GMT* geometric mean titer, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2

GMTs of nAb, anti-S1 IgG and anti-RBD IgG remained higher in younger participants than in older participants at month 6.

As with other disease vaccines, antibody waning following vaccination against SARS-CoV-2 is expected [17, 18]. In this trial, there was a gradual decline in GMTs of neutralizing, anti-S1 IgG and anti-RBD antibodies, though humoral immune responses were observed through 6 months of follow-up. These results are comparable to other SARS-CoV-2 vaccines (including BNT162b2), which have also demonstrated waning antibody titers over the 6 months post-vaccination [19–22]. As T-cell response is thought to play a role in preventing reinfection, particularly in the context of waning antibody titers, these reduced titers may not correspond to a less efficacious vaccine [23]. Waning antibody titers of other mRNA SARS-CoV-2 vaccines have prompted the administration of booster doses after 6 months, including BTN162b2 [24, 25], and boosters would likely be needed for BNT126b1 if it were being further developed.

LIMITATIONS

This study is limited by its small sample size of adult Chinese participants only, which limits generalizability to other populations. Additionally, we did not measure cross-neutralizing antibody levels against recently emerged variants of concern during the follow-up period, and persistence of cellular response was not determined in the older participants. A key limitation of the findings in this report is that, of the two BNT162 vaccines in this pipeline, though the immunogenicity was comparable with BNT162b2, the BNT162b1 vaccine is less promising in terms of systemic reactogenicity and therefore has not been further developed.

CONCLUSION

The current data confirm a favorable safety profile of the mRNA-based SARS-CoV-2 BNT162b1 vaccine candidate in younger and older participants over a 6-month period. The study also extends our understanding of immune persistence and the safety of the BNT162b1 vaccine in the context of other vaccines in the BioNTech pipeline.

Table 1 Antibody persistence 3 and 6 months after the first dose of BNT162b1 vaccination

	Three months after the first dose			Six months after the first dose					
	Younger participants (aged 18–55 years)			Younger participants (aged 18–55 years)			Older participants (65–85 years)		
	10 µg (*N* = 24)	30 µg (*N* = 24)	Placebo (*N* = 24)	10 µg (*N* = 24)	30 µg (*N* = 24)	Placebo (*N* = 22)	10 µg (*N* = 23)	30 µg (*N* = 23)	Placebo (*N* = 23)
Virus neutralizing antibody									
GMT	55 (38–79)	87 (64–118)	5 (5–5)	16 (11–24)	27 (20–37)	5 (5–5)	10 (7–14)	21 (13–32)	5 (5–5)
GMFI	11.0 (7.6–15.8)	17.4 (12.9–23.6)	1.0 (1.0–1.0)	3.3 (2.3–4.7)	5.5 (4.1–7.4)	1.0 (1.0–1.0)	2.0 (1.4–2.8)	4.1 (2.7–6.4)	1.0 (1.0–1.0)
SCR	21 (88; 68–97)	24 (100; 86–100)	0 (0; 0–14)	14 (58; 37–78)	20 (83; 63–95)	0 (0; 0–15)	7 (30; 13–53)	14 (61; 39–80)	0 (0; 0–15)
Anti-S1 IgG									
GMT	27,143 (21,023–35,044)	31,584 (26,379–37,817)	50 (50–50)	4,169 (2,979–5,836)	5,693 (4,412–7,346)	55 (48–63)	2,224 (1,566–3,158)	4,970 (3,626–6814)	61 (46–81)
GMFI	488.9 (359.3–665.2)	532.2 (371.3–762.7)	0.9 (0.8–1.1)	75.1 (50.1–112.6)	95.9 (66.9–137.6)	1.0(0.9–1.1)	42.7 (29.5–61.8)	90.6 (64.5–127.4)	1.0 (0.9–1.1)
SCR	24 (100; 86–100)	24(100; 86–100)	0 (0; 0–14)	24 (100; 86–100)	24 (100; 86–100)	0 (0; 0–15)	23 (100; 85–100)	23 (100; 85–100)	0 (0; 0–15)
Anti-RBD IgG									
GMT	40,236 (33,000–49,060)	43,051 (38,768–47,807)	60 (50–73)	8250 (6186–11,001)	9608 (7410–12,459)	62 (50–76)	4114 (2717–6231)	7188 (5139–10,054)	55 (48–62)
GMFI	804.7 (660.0–981.2)	815.0 (706.6–940.0)	1.1 (1.0–1.1)	165.0 (123.7–220.0)	181.9 (145.9–226.8)	1.1 (0.9–1.3)	69.8 (48–102)	104.6 (65.8–166.3)	0.8 (0.6–1.0)
SCR	24 (100; 86–100)	24 (100; 86–100)	0 (0; 0–14)	24 (100; 86–100)	24 (100; 86–100)	0 (0; 0–15)	23 (100; 85–100)	22 (96; 78–100)	0 (0; 0–15)

Data are GMT (95% CI) and number of participants (%, 95% CI) for SCR. The participants received two doses of the BNT162b1 vaccine 21 days apart

anti-RBD IgG antibody to receptor binding domain, *anti-S1 IgG* antibody to S1 protein, *CI* confidence interval, *GMT* geometric mean titer, *GMFI* geometric mean fold increase, *N* number of participants included in each treatment group with determinate immunogenicity results, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2, *SCR* seroconversion rate

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Compliance with Ethics Guidelines. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol was approved by Chinese NMPA and the institutional review board of the Jiangsu Provincial Center of Disease Control and Prevention. Informed consent was obtained from all individual participants included in the study.

Data Availability. We support sharing of individual participant data. The individual participant data that underlie the results reported in this article (text, table, figure, and extended data) will be shared after de-identification. The raw data will be available for 1 year after the publication of this article. Researchers that provide a scientifically sound proposal will be allowed access to the individual participant data. Proposals should be directed to jszfc@vip.sina.com or aimin.hui@fosunpharma.com. All code used to produce the results can be accessed by sending a scientifically sound proposal to jszfc@vip.sina.com or aimin.hui@fosunpharma.com. The code will be available with the raw data.

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