Evaluation of Safety and Anti-RBD IgG SARS-CoV-2 after Indovac Administration in Depok

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Received 30 March 2023; Accepted 23 July 2023
https://doi.org/10.23886/ejki.11.393.118

Abstract

The WHO declared the COVID-19 pandemic on March 11, 2020, then several centres developed Covid-19 vaccines. The Indovac vaccine contains SARS-CoV-2 RBD antigen adjuvanted with Alum and CpG1018. This article reported Jakarta Centre Phase 1 trial results of the safety and immunogenicity of Indovac in Kota Depok in February 2022 - January 2023 . This study is a randomised, observer-blinded, active-control (Sinovac) clinical trial. The study included 175 healthy adults aged 18–70 and 75 participants were enrolled by the Jakarta centre. Two vaccine doses were given 28 days apart. Four vaccine formulas were tested. Safety evaluations included solicited and unsolicited adverse events (AE) up to 28 days post-injection. SARS-CoV-2 anti-RBD IgG was tested before, 14, and 28 days after second injection to determine immunogenicity. Most solicited AEs were injection site pain. Local pain was highest in the RLCL group after the first dose (38.62%) and RHCH after the second dose (23.08%). 13.33% and 6.67% of control group subjects experienced local pain after the first and second injections, respectively. RHCL has the highest seroconversion (100%) after two injections. Anti-RBD IgG responses increased (p<0.005) in all groups and plateaued 28 days after the second dose injection. In conclusion, Indovac was safe and immunogenic in Jakarta.

Keywords: Indovac, Vaccine, COVID-19, RBD, CpG1018.

Evaluasi Keamanan dan Anti-RBD IgG SARS-CoV-2
Setelah Pemberian Indovac di Kota Depok

Abstract


Introduction

The World Health Organization declared the outbreak of acute respiratory syndrome as the Covid-19 pandemic on 11 March 2020. The syndrome caused high morbidity and mortality due to its highly contagious nature with airborne spread. The current virus, SARS-CoV-2, was considered a new beta coronavirus with its genome sequence sharing 79.5% sequence identity to SARS-CoV. Up to this day, numerous mutations have been recorded with various virulence. The virus has infected more than 675 million people with around 6.87 million deaths worldwide. Meanwhile, in Indonesia, COVID-19 is diagnosed in 6.74 million people with 161,000 deaths. Despite the slowing case growth and lowering mortality rate due to various efforts, the virus is still a various issue and needed further precautions.

Precautions had been taken to prevent the disease from spreading. Personal hygiene, face masks, airborne precaution for healthcare workers, social distancing and policies had been held to avoid the high infection cases, but it was not enough to suppress the cases number. Rapid vaccine development was done in different centres to reach herd immunity amongst the public, with different brands and types of vaccines are known available to the public. The most common vaccine in the market for COVID-19 are commonly the traditional vaccine consisting of inactivated virus, or the quite-novel mRNA vaccines to produce protein to invoke immune response after use. However, further vaccine development is always welcome in battling the pandemic, one of which is the RBD-targeting subunit protein vaccine. Similar vaccine has been clinically trialled, such as Corbevax which have reached phase 2 of its clinical trial with promising results.

Indovac is a protein recombinant subunit vaccine developed by PT Bio Farma using similar mechanism. The vaccine used the SARS-CoV-2 receptor-binding domain as an antigen which made by the Texas Children’s Hospital Centre for Vaccine Development (TCH-CVD) at Baylor College of Medicine (BCM). The trial evaluates the product’s safety and immunogenicity in Indonesia. This article reports the result of the trial in the Jakarta centre.

Methods

Study Design and Participants

This study is a phase 1 randomised controlled trial with observer blinded. The trial was run at two centres in Indonesia: the Child Health Department of the Faculty of Medicine Universitas Indonesia, Jakarta and the Faculty of Medicine Universitas Diponegoro, Semarang. The sampling was conducted in two health care centres in Jakarta (Puskesmas Tapos and Puskesmas Cilangkap). in February 2022 - January 2023.

Eligible participants were healthy subjects aged 18-70 years. Exclusion criteria were participants with confirmed Covid-19 history, prior COVID-19 vaccination history, pregnant and lactating women, and an uncontrolled chronic illness. Prior to enrolment, participants were screened for any physical and laboratory abnormalities. Participants were also tested for SARS-CoV-2 PCR test from a pharyngeal sample. Those with anomalies were excluded.

The sample size was based on the phase 1 clinical studies principle; to evaluate safety and dosage, a small number of healthy adults were recruited. In this phase 1 study, 175 subjects were involved, with 35 for each interventional group. These numbers were divided into two subset studies: the main study for safety and immunogenicity evaluation and the cellular immunity subset.

Signed informed consent was obtained prior to screening for included and excluded participants. The trial was conducted following the latest Edinburg, Scotland revision of the Declaration of Helsinki, ICH Good Clinical Practice guidelines, and local regulatory requirements. This study was approved by Universitas Indonesia Ethical Committee (Protocol Number 22-01-0112).

Procedures

Subjects were scheduled to get two doses of the investigational product 28 days apart. Subjects were given an inclusion number based on recruit order by the unblinded team; the blinded team did not have any data of the subject group code. Each dose administration was followed by a safety and serology assessment. Safety surveillance was done by giving the subject a diary card to record any local or systemic adverse event 28 days following each dose of vaccine. Serious adverse events (SAE) were monitored since subjects enrolled on trial until six months after the last dosing. Monthly follow-up by phone was held to monitor any subject’s complaint. For the main study subset, additional safety was assessed by laboratory markers to monitor any organ anomalies after immunisation. This was scheduled seven days after the first dose and 14 days after the second dose. Serology evaluation was run at baseline, 14 days and 28
days after the second dose. Blood samples were taken to evaluate IgG anti-RBD SARS-CoV-2 and IgG-neutralising antibodies of SARS-CoV-2. Anti-RBD IgG seropositive is defined as titer ≥50 AU/mL, whereas seroconversion is defined as a four-fold increasing anti-RBD IgG titer compared to baseline.

**Vaccine and Control**

The randomisation was assigned by an unblinded team which held the generated randomisation list. Total subjects were divided into five groups, one active control and four different formulas of vaccine product (Table 1), to the ratio of 1:1:1:1:1.

**Table 1. Composition of Investigation Products**

<table>
<thead>
<tr>
<th>Composition</th>
<th>Formula A (RLCL)</th>
<th>Formula B (RLCH)</th>
<th>Formula C (RHCL)</th>
<th>Formula D (RHCH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SARS-CoV-2 RBD subunit recombinant protein</td>
<td>12.5 μg</td>
<td>12.5 μg</td>
<td>25 μg</td>
<td>25 μg</td>
</tr>
<tr>
<td>Aluminium hydroxide</td>
<td>750 μg</td>
<td>750 μg</td>
<td>750 μg</td>
<td>750 μg</td>
</tr>
<tr>
<td>CpG 1018</td>
<td>750 μg</td>
<td>1500 μg</td>
<td>750 μg</td>
<td>1500 μg</td>
</tr>
<tr>
<td>Buffer</td>
<td>2.226 mg sodium chloride &amp; 0.923 mg tris(hydroxymethyl) aminomethane.</td>
<td>2.204 mg sodium chloride &amp; 0.914 mg tris(hydroxymethyl) aminomethane.</td>
<td>2.226 mg sodium chloride &amp; 0.923 mg tris(hydroxymethyl) aminomethane.</td>
<td>2.204 mg sodium chloride &amp; 0.914 mg tris(hydroxymethyl) aminomethane.</td>
</tr>
</tbody>
</table>

RLCL= Dose RBD Low, CpG Low; RLCH = Dose RBD Low, CpG High; RHCL = Dose RBD High, CpG Low; and RHCH = Dose RBD High, CpG High

The vaccine candidate was based on recombinant protein-based RBD protein. It was based on the sequence of the wild-type SARS-CoV-2 RBD amino acid, representing residues 331-549 of the spike (S) protein (GenBank: QHD43416.1) of the Wuhan-Hu-1 isolate (GenBank: MN908947.3). The DNA encoding SARS-CoV-2 RBD was codon optimised based on yeast codon preference, synthesised, and cloned into the yeast expression vector pPICZA using animal-free chemicals by GenScript to create recombinant SARS-CoV-2 RBD protein. The recombinant plasmid DNA was transformed into P. pastoris X-33. The clone with the highest expression yield was chosen for making the Research Cell Bank under the approved NS-S2RBD-21-0003 after being induced with 0.5-1.0% methanol in a 10 mL medium. For enhancing immunogenicity, adjuvants were added. CpG 1018 and aluminium hydroxide adjuvants were used in inducing antibodies that neutralised wild-type live viruses while minimising Th2-biased responses with no vaccine-related adverse effects.

The control product was the Biofarma COVID-19 vaccine which was produced through inoculation of novel coronavirus (CZ02 Strain) into the African Green Monkey Kidney Cell (Vero Cell). The vaccine candidate and control product had different packaging; therefore, it was not possible to run a double-blind study. Active control was considered more beneficial than a placebo to protect controlled subjects from getting infected, and according to the WHO Expert Panel, this practice would not harm the Declaration of Helsinki or previous guidance by the WHO.

**Statistical Analysis**

Statistical analysis was run using Fisher’s test for categorical outcomes such as seropositive, seroconversion, and adverse events occurrence between groups and ANOVA test for numeric outcomes such as GMT of IgG anti-RBD SARS-CoV-2. Comparison for the geometric mean of antibody titre was run after the data were log-transformed. Non-reactive IgG anti-RBD SARS-CoV-2 will be counted to 21 based on the CMIA test’s lower limit of quantitation. Statistical analysis was done using SPSS 20.0.

**Results**

From 18 February to 30 May 2022, 111 participants were screened in the Jakarta centre (Figure 1). The Jakarta centre was responsible for the recruitment of 75 subjects consisting of all cellular immunity subsets (50 subjects) and the main study subset (25 subjects). The dropped out were 10 participants due to loss-to-follow up or
participants withdrawal from the study, thus a total of 65 subjects were included in the final analysis. Both subsets’ subjects were assessed for safety up to 28 days after their last immunization unless they didn’t show up for a follow-up visit. Two subjects from cellular immunity subsets were terminated due to admitting after enrolment to have already had another Covid-19 vaccine before the trial period and one subject from the main study subset did not show up for their 14-day follow-up after the first dose, therefore these subjects were not included in the safety analysis.

Figure 1. Subjects disposition in Jakarta Centre
Table 2. Characteristics of the Subjects

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control n=15</th>
<th>RLCL n=15</th>
<th>RLCH n=15</th>
<th>RHCL n=15</th>
<th>RHCH n=15</th>
<th>Total n=75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age/years (SD)</td>
<td>28.13 (9.81)</td>
<td>28.60 (11.94)</td>
<td>28.07 (7.64)</td>
<td>33.13 (14.53)</td>
<td>38.13 (10.86)</td>
<td>31.21 (11.59)</td>
</tr>
<tr>
<td>Mean height/m (SD)</td>
<td>161.60 (5.57)</td>
<td>165.88 (7.06)</td>
<td>164.48 (11.17)</td>
<td>160.99 (13.14)</td>
<td>159.47 (8.61)</td>
<td>162.48 (10.94)</td>
</tr>
<tr>
<td>Mean weight/kg (SD)</td>
<td>53.33 (7.39)</td>
<td>60.70 (13.45)</td>
<td>57.56 (11.17)</td>
<td>57.64 (8.32)</td>
<td>58.52 (3.48)</td>
<td>57.55 (10.44)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>20.44 (2.78)</td>
<td>21.96 (4.23)</td>
<td>21.35 (4.25)</td>
<td>22.31 (5.01)</td>
<td>23.10 (3.48)</td>
<td>21.83 (4.01)</td>
</tr>
<tr>
<td>Sex n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>11 (73.33)</td>
<td>13 (86.67)</td>
<td>12 (80.00)</td>
<td>13 (86.67)</td>
<td>8 (53.33)</td>
<td>57 (76.00)</td>
</tr>
<tr>
<td>Female</td>
<td>4 (26.67)</td>
<td>2 (13.33)</td>
<td>3 (20.00)</td>
<td>2 (13.33)</td>
<td>7 (46.67)</td>
<td>18 (24.00)</td>
</tr>
<tr>
<td>Previous Education n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary school (some)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td>1 (6.67)</td>
<td>2 (13.33)</td>
<td>2 (13.33)</td>
<td>5 (6.67)</td>
</tr>
<tr>
<td>Primary school (completed)</td>
<td>4 (26.67)</td>
<td>3 (20.00)</td>
<td>3 (20.00)</td>
<td>1 (6.67)</td>
<td>2 (13.33)</td>
<td>13 (17.33)</td>
</tr>
<tr>
<td>Junior high school</td>
<td>4 (26.67)</td>
<td>5 (33.33)</td>
<td>1 (6.67)</td>
<td>5 (33.33)</td>
<td>7 (46.67)</td>
<td>22 (29.33)</td>
</tr>
<tr>
<td>Senior high school</td>
<td>7 (46.67)</td>
<td>7 (46.67)</td>
<td>9 (60.00)</td>
<td>6 (40.00)</td>
<td>4 (26.67)</td>
<td>33 (44.00)</td>
</tr>
<tr>
<td>College or university (diploma)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td>1 (6.67)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td>1 (1.33)</td>
</tr>
<tr>
<td>NA</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td>1 (6.67)</td>
<td>1 (1.33)</td>
</tr>
</tbody>
</table>

Abbreviations: N= number of participants, SD = Standard deviation

The most common adverse event is local pain. In the vaccine group, 32.14% and 37.31% of participants experienced local pain following the first and second injections, respectively. Local pain was most prevalent in the RLCL group after the first dose (38.62%) and RHCH group after the second dose (23.08%). Local pain was experienced by 13.33% and 6.67% of control group subjects following the first and second injections, respectively. Unsolicited adverse events vary across groups, the most common complaint is epigastric pain which occurred days after immunization, therefore it was considered a coincidental event. No reported severe intensity of adverse events. There were no reported SAEs throughout the trial period. Additional laboratory safety evaluation showed no significant abnormalities after injections.

![Figure 2. Adverse Event Following Immunisation after First Dose (A) and Second Dose (B)](image-url)
Figure 3. IgG Anti-RBD (AU/mL) SARS-CoV-2 Increment after Two Doses.

Table 3. IgG anti-RBD SARS-CoV-2 Antibody Titre in Different Groups

<table>
<thead>
<tr>
<th>Serology Test Period</th>
<th>Serology Outcome</th>
<th>Control (n=15)</th>
<th>RLCL (n=12)</th>
<th>RLCH (n=12)</th>
<th>RHCL (n=15)</th>
<th>RHCH (n=13)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Seropositive rate n(%)</td>
<td>14 (93.33)</td>
<td>11 (91.67)</td>
<td>12 (100)</td>
<td>14 (93.33)</td>
<td>13 (100)</td>
<td>0.539*</td>
</tr>
<tr>
<td></td>
<td>GMT (AU/mL) (95% CI)</td>
<td>539.85 (166.8-1747.43)</td>
<td>1015.33 (248.71-4145.72)</td>
<td>524.59 (141.45-1946.26)</td>
<td>484.32 (185.23-1266.19)</td>
<td>660.59 (261.82-1666.48)</td>
<td>0.878**</td>
</tr>
<tr>
<td>14 days after the 2nd dose</td>
<td>Seropositive rate n(%)</td>
<td>15 (100)</td>
<td>12 (100)</td>
<td>12 (100.00)</td>
<td>15 (100)</td>
<td>13 (100)</td>
<td>1.000*</td>
</tr>
<tr>
<td></td>
<td>GMT (AU/mL) (95% CI)</td>
<td>1650.59 (889.00-3064.78)</td>
<td>22098.73 (15024.50-32508.73)</td>
<td>22132.09 (15100.80-32441.43)</td>
<td>20109.26 (8715.65-46398.08)</td>
<td>23936.47 (16611.16-34490.54)</td>
<td>&lt;0.005**</td>
</tr>
<tr>
<td>28 days after the 2nd dose</td>
<td>Seropositive rate n(%)</td>
<td>15 (100)</td>
<td>12 (100)</td>
<td>12 (100)</td>
<td>15 (100)</td>
<td>13 (100)</td>
<td>1.000*</td>
</tr>
<tr>
<td></td>
<td>GMT (AU/mL) (95% CI)</td>
<td>1387.85 (748.00-2575.13)</td>
<td>22208.71 (14658.85-33651.16)</td>
<td>21247.08 (13495.84-33450.30)</td>
<td>19269.48 (8814.55-46398.08)</td>
<td>23974.91 (16455.08-34930.11)</td>
<td>&lt;0.005**</td>
</tr>
</tbody>
</table>

*Fisher’s Test  
**ANOVA test with log-transformed data

In the control group, antibody decrement occurred in one subject within 28 days after the second dose (538.7 to 337.1) although its 14 days titre indeed 4-fold increased from baseline. This also could be seen in the RHCL group where antibody titre decreased 28 days after the second dose (28974.8 to 23045.3). A decrease of seropositive rate in the group RLCH and RHCL occurred due to the subject’s antibody reaching the peak measured titre (greater than 40,000 AU/ml). Furthermore, one subject from the RLCH group had a maximum antibody titre to be measured at baseline, therefore any increment was undetected due to the limitation of the instrument.

Discussion

Covid-19 persists as a global health threat today. Globally, 6.8 million deaths and over 754 million confirmed cases had been reported as of 8 February 2023. Even after the pandemic was declared two years ago, Indonesia still reported the highest number of new cases in Southeast Asia (7589 new cases; 2.8 new cases per 100,000) from 9 January to 5 February 2023.\(^9\) This number has significantly decreased because of public health and social measures (PHSMs), immunization against the Covid-19 infection, and, to a lesser extent, infection-induced immunity. Development of the Covid-19 vaccine is still ongoing to establish...
a durable and broadly protective immunity, it leads to transmission reduction which will help against the emergence of new variants of concern and safe health and economic consequences.\textsuperscript{10}

Several vaccines have been developed against SARS-CoV-2 based on the following vaccine platform: mRNA-based, viral vector, whole-pathogen inactivated virus, and a subunit vaccine that contain a fragment of the pathogen. All reported vaccine candidates so far presented promising efficacy. Moreover, the subunit vaccine’s lack of genetic materials makes them safe and non-infectious/non-viable making them favourable to be produced. The protein subunit vaccine was the highest against RBD at 87.3\% (95\% CI 0.671-0.892) four weeks after the first dose and 95.6\% (95\% CI 0.901-0.375) four weeks after the second dose.\textsuperscript{11} Several diagnostic methods have started to target the S protein, especially RBD. In order to identify SARS-CoV-2 IgG in human serum, the Enzyme-Linked Immunosorbent Assay (ELISA) method was used to apply the SARS-CoV-2 RBD IgG test as an antibody test for COVID-19. For identifying those who have an adaptive immune response to SARS-CoV-2, the RBD IgG test was created. RBD is furthermore noted as a potential target for therapeutic interventions and vaccine development. The RBD is a target for vaccine research as well. Many recombinant subunit vaccines, such as AdmrsSC-2f, S-RBD protein vaccine of China, ZF2001 employing dimeric fragment of RBD, VIR-7831, AZD7442, or LY-CoV555, contain the RBD of SARS-CoV-2 and Fc fragment of human IgG. 17 RBD is also used as the vaccine target by more well-known commercial vaccines like Moderna mRNA-1273 and BioNTech-Pfizer BNT162b1, which produce protein using mRNA.

Subunit recombinant protein vaccine is known to be less demanding and successful in preventing infectious diseases. Yeast has been selected as the preferred host organism for the manufacture of recombinant protein antigens due to its qualities as a host organism through microbial fermentation. These properties allow for robust production with cheap costs and expandable capacity. RBD SARS-CoV2, which is created through the fermentation of \textit{Pichia pastoris}, is used in this investigational product.\textsuperscript{6}

The SARS-CoV-2 protein recombinant subunit vaccine in this trial used RBD as an antigen and was adjuvanted with CpG1018 and Aluminium Hydroxide. Adjuvants have an essential role in inducing a specific immune response, IgG, and NAbs. The non-adjuvanted vaccines display immunopathologic reactions such as high fatigue, vomiting, fever, myalgia, diarrhoea, and redness. The alum-adjuvanted CoV vaccine had the lowest systemic side effects among other adjuvants. A combination of CpG and Alum adjuvants show myalgia as their side effect with OR 2.42 (95\% CI 0.13-44.50).\textsuperscript{12}

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A significant humoral immune response and the release of Th2-biased cytokines (e.g., IL-4, IL-6, IL-10) are typically induced by aluminium-based formulations. CpG adjuvants are solid stimulators of the innate immune system via Toll-like receptor-9 activation. TLR9 agonists directly stimulate the activation and maturation of plasmacytoid dendritic cells and promote the differentiation of B cells into antibody-producing plasma cells.\textsuperscript{13}

This product formula is similar to the COVID-19 vaccine Corbevax which has been approved for EUA on 28 December 2021 in India. In Corbevax Phase 1/2, 360 subjects were vaccinated with different formulations of RBD SARS-CoV-2 doses of 15\,µg, 25\,µg, and 50\,µg. They received 0.5\,mL 2-dose scheduled within 28 days. Six-month follow-up data showed promising immune response by increasing CpG1018 adjuvant to 750\,µg. Adverse events were reported in 42 subjects, and none was serious. Similar to Corbevax, there is no reported SAE and most AEs are mild symptoms without severe intensity with promising findings and seropositivity rate with high rate of 4-fold increasing antibody titers for anti-RBD. On the other hand, the most AE reported in this trial was local pain while in the Corbevax trial was pyrexia.\textsuperscript{14}

Our findings in this study showed that most of the population in Kota Depok had already had immunity against SARS-CoV-2, meaning that they may have evolved an asymptomatic infection prior to enrolment. This study finds seroconversion is highest in the RHCL group (100.00\%) after two injections. Anti-RBD IgG concentrations after two doses increased significantly in all groups and plateaued up to 28 days after the second dose. This result is the same as with Corbevax Phase 1/2 trial, they presented that anti-RBD IgG concentration plateaued after the second dose.
dose between 42-56 days after the second dose. However, the highest seroconversion was found in the formulation of 25 μg RBD, 750 μg Aluminium Hydroxide, and 500 μg CpG1018.14

Our study showed a significant difference between the control and investigational product in IgG anti-RBD SARS-CoV-2. Despite this, it is still unclear whether nAbs are related to anti-RBD antibody levels, given there are conflicting reports on this topic.15 Nevertheless, Corbevax showed a promising correlation between nAb-titers and anti-RBD IgG concentration.14 Further investigation of neutralising antibody is needed to ensure the binding antibody found in these trials correlate with its protection against SARS-CoV-2.

Conclusion
In this phase I trial for subjects in Depok, Indovac showed as a safe and immunogenic vaccine against Covid-19. However, additional analysis regarding neutralising antibodies against the virus is still needed to be reported.

Acknowledgement
The authors would like to extend their gratitude to the following colleagues for their contributions to the study: the staff of Tapos and Cilandak Primary Health Centre, dr. Windri Retnaningdyah, Hermita Santi Simajuntak, Maria Zemlia, Dwi Novyanti, Hani Sabrina Rusdianti, Yuni Yudha Aprilia, M. Hanif Triananda, Kevin Sebastian Santoso.

Conflict of Interests and Funding Sources
PT Bio Farma, Indonesia, funded this study. The funding body was not engaged in the analysis and interpretation of the data performed by the investigators.

References