Clinical Study Protocol

A Phase I/II, First-in-human, Observer-blinded, Randomized, Placebo-controlled, Parallel Group Study to Evaluate the Safety and Immunogenicity of TAP-COVID-19 SARS-CoV-2 Vaccine with CpG Adjuvant in Healthy Adults Aged 18-49 and 50-85

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1 SYNOPSIS

Protocol Title:	A Phase I/II, First-in-human, Observer-blinded, Randomized, Placebo-controlled, Parallel Group Study to Evaluate the Safety and Immunogenicity of TAP-COVID-19 SARS-CoV-2 Vaccine with CpG Adjuvant in Healthy Adults Aged 18-49 and 50-85
Study Phase:	Phase I/II
Objectives:	Primary Objective: • To assess the safety and reactogenicity of two doses of TAP-COVID-19 vaccine with Cytosine PhosphoGuanine (CpG) adjuvant for 7 days post vaccination compared with placebo as determined by solicited local and systemic reactogenicity Secondary Objectives: • To compare the frequency of unsolicited adverse events (AEs) of each dose of TAP-COVID-19 vaccine with CpG adjuvant through Day 43 and serious adverse events (SAEs), medically attended adverse events (MAAEs), new onset chronic diseases (NOCDs), and adverse events of special interest (AESIs) through Day 365 Comparisons include: o High dose (45 µg TAP-COVID-19 vaccine + 0.5 mg CpG) to placebo o Low dose (15 µg TAP-COVID-19 vaccine + 0.5 mg CpG) to placebo o High dose (45 µg TAP-COVID-19 vaccine + 0.5 mg CpG) to low dose (15 µg TAP-COVID-19 vaccine + 0.5 mg CpG) • To evaluate the immunogenicity of TAP-COVID-19 vaccine with CpG adjuvant compared with placebo in terms of antibody assessed by geometric mean titers (GMTs) of both spike receptor binding domain (RBD) IgG and IgM antibodies and neutralizing antibody response, geometric mean fold rise (GMFR) in neutralizing titer from baseline in all treatment groups at Days 8, 22, 29, 43, 90, 181, 273, and 365 relative to baseline Exploratory Objectives: • To assess cellular immunity by measuring the numbers of cytokine producing CD4+ and CD8+ T-cells from peripheral blood mononuclear cells (PBMCs) response to vaccine in all treatment groups at Days 8, 22, 29, 43, 90, 181, 273, and 365 compared to baseline • To assess the immunogenicity of the RBD and Fc component of the vaccine
Endpoints:	Primary Endpoints: Occurrence of Solicited AEs: • Solicited administration site reactions (eg, pain, tenderness, erythema/redness, induration/swelling) during the 7-day follow-up period after each vaccination (Day 1-8 and Day 22-29) • Solicited systemic events (eg, fever, nausea/vomiting, diarrhea, headache, fatigue, myalgia) during the 7-day follow-up period after each vaccination (Day 1-8 and Day 22-29) Secondary Endpoints: Safety: • Unsolicited AEs, MAAEs, and AESIs up to Day 43 • SAEs, MAAEs, NOCDs, and AESIs up to Day 365 (approximately 1 year after first vaccination) Immunogenicity: Vaccine enzyme-linked immunosorbent assay of both spike receptor binding domain (RBD) IgG and IgM antibodies and neutralizing antibody titers for each treatment group: • GMT at baseline and Days 15, 22, 43, 90, 181, 273, and 365 • GMT ratio ($GMT_{placebo}/GMT_{TAP\text{-}COVID\text{-}19}$) at baseline and Days 22, 29, 43, 90, 181, 273,

	and 365 • GMFR at Days 8, 22, 29, 43, 90, 181, 273, and 365 relative to baseline • Seroconversion rates on Days 8, 15, 22, 29, 43, 90, 181, 273, and 365. Seroconversion is defined as the proportion of subjects at the respective time point that have detectable antibodies (IgG and IgM) against SARS-CoV-2 Spike Protein RBD following challenge with vaccine (and potentially by natural asymptomatic or symptomatic infection by the virus in case of a placebo subject). • Geometric mean increase (GMI) on Days 8, 22, 29, 43, 90, 181, 273, and 365 Exploratory Endpoints: Cellular immunity: • The number of cytokine producing CD4+ and CD8+ T-cells from PBMCs responsive to vaccine antigens in all treatment groups on Days 8, 22, 29, 43, 90, 181, 273, and 365 compared to baseline Immunogenicity: • Anti-RBD and anti-Fc antibodies at baseline and Days 8, 15, 22, 29, 43, 90, 181, 273, and 365
Study Design:	This is a first-in-human (FIH), observer-blinded, randomized, placebo-controlled, parallel group study to evaluate the safety and immunogenicity of TAP-COVID-19 vaccine with CpG adjuvant in healthy adult subjects in 2 age groups, Part A (18-49 years) and Part B (50-85 years). A study schematic is presented in Figure 4-1. PART A and PART B: Subjects will be screened up to 14 days (Day -14 to Day -1) before randomization. Overall, approximately 90 eligible healthy adults ages 18-49 years (inclusive) will be enrolled for Part A and 90 eligible healthy adults ages 50-85 years will be enrolled for Part B. Sentinel dosing will be utilized in this FIH study. Sentinel cohorts will be used for the following groups: - Part A (18-49 years) low dose (15 µg TAP-COVID-19 vaccine + 0.5 mg CpG) - Part B (50-85 years) low dose (15 µg TAP-COVID-19 vaccine + 0.5 mg CpG) - Part A (18-49 years) high dose (45 µg TAP-COVID-19 vaccine + 0.5 mg CpG) - Part B (50-85 years) high dose (45 µg TAP-COVID-19 vaccine + 0.5 mg CpG) Three sentinel subjects from each part will be randomized 2:1 (active:placebo). The independent Safety Review Committee (iSRC) will review the safety and tolerability data for the sentinel subjects through Day 8 prior to enrollment of the remaining cohort subjects randomized 2:1 (active:placebo). When all subjects in Part A (18-49 years) low dose have received the first vaccination and have all safety data through Day 8, the iSRC will convene and review the safety data to ensure that there are no safety concerns and that none of the Study Halting Rules have been met before recommending that the study enroll Part A high dose and Part B (50-85 years) low dose. When all subjects in Part B (50-85 years) low dose have received the first vaccination and have all safety data through Day 8, the iSRC will convene and review the safety data to ensure that there are no safety concerns and that none of the Study Halting Rules have been met before recommending that the study enroll Part B high dose. The iSRC will convene and review the safety data when a minimum of 23 subjects have completed Day 29 after the second vaccination for Part A (low and high dose) and for Part B (low and high dose) to ensure that there are no concerns. Both Part A (18-49 years) and Part B (50-85 years) will be randomized in a 2:1 ratio (active:placebo) for each treatment dose (15 µg and 45 µg TAP-COVID-19 vaccine + 0.5 mg CpG) for a total of 90 subjects per Part (30 subjects 15 µg TAP-COVID-19 vaccine + 0.5 mg CpG:30 subjects 45 µg TAP-COVID-19 vaccine + 0.5 mg CpG:30 subjects placebo). Treatment A: TAP-COVID-19 vaccine (15 µg) + CpG (0.5 mg) intramuscular (IM) injection

	on Day 1 and Day 22 (±3 days) Treatment B: TAP-COVID-19 vaccine (45 μg) + CpG (0.5 mg) IM injection on Day 1 and Day 22 (±3 days) Treatment C: Placebo (buffered saline solution) IM injection on Day 1 and Day 2 (±3 days) Study vaccine will be prepared by an unblinded site pharmacist and administered at the clinical research site on Day 1 and Day 22 (±3 days) by unblinded clinical research unit (CRU) personnel. Subjects will be observed for immediate AEs and/or reactogenicity for approximately 60 minutes after administration of vaccine. Subjects will be provided with a Diary Card and will be trained to record specifically elicited systemic and local symptoms daily as well as any additional AEs during the 7-day follow-up period after each vaccination. Visits will be conducted at the clinical site on an outpatient basis or as a telephone visit per the Schedule of Assessments and Procedures. Subjects will participate in the study for approximately 1 year from the first dose. AEs and concomitant medications will be captured through Day 43. Blood and serum samples for safety laboratory tests, RBD IgG and IgM antibodies and neutralizing antibody titers, cell-mediated immunity, and other future biomedical research will be obtained at baseline and before administration of vaccine dose 2 and after each vaccination per the Schedule of Assessments and Procedures. SAEs, MAAEs, NOCDs, and AESIs only will be captured after Day 43 to study completion (Day 365 [approximately 1 year after first vaccination]). Prior to receiving a second dose of vaccine, subjects will have the following assessments performed to ensure eligibility: vital signs (including temperature), review of clinical laboratory test results to date, nasopharyngeal swab Day 15 to check for SARS-CoV-2 infection (reverse transcription polymerase chain reaction [RT-PCR] result must be received by the CRU and negative prior to the second vaccine administration), medical history since last visit including AE assessment for SAEs, Grade 3 AEs, or AESIs that are possibly, probably, or definitely related to study vaccine without a plausible alternative explanation, targeted physical examination, recheck of eligibility criteria, and pregnancy test (as applicable). Subjects will be monitored for SARS-CoV-2 exposure for potential asymptomatic infection throughout the study. • If a subject has a positive or borderline ELISA anti-N IgG result, sites should have the subject return for an unscheduled PCR. If the ELISA is positive and the PCR is negative, the sites should follow the subjects using the standard of care under Investigator discretion, retesting ELISA at the next study visit(s) or sooner (per the Investigator's decision). • If the subject has a positive or borderline ELISA anti-N IgG AND a positive PCR test, the clinical sites should bring the subjects back for repeat PCR testing as described below. • The clinical sites should continue to collect PCR tests if a subject is experiencing possible COVID-19 symptoms, or had possible exposure to SARS-CoV-2 (ie, close contact tests positive for SARS-CoV-2). Testing will occur every 2 weeks for a total of 4 weeks (if 2 consecutive negative tests) or until negative (x2) after a positive result. Positive results will be reported as an AESI and subjects followed for disease severity, duration, and outcome. Subjects who are seropositive for SARS-CoV-2 and asymptomatic will be allowed to enroll into Parts A and B of the study as long as the subject is RT-PCR negative. <u>Interim Safety Data Reviews</u>: For all of the sentinel groups, the iSRC will meet to review the sentinel subjects' safety and tolerability data through Day 8. In the event that iSRC has not met for the post Day 8 review because the entire sentinel group (n = 3) has not completed Day 8 before a sentinel subject

	is to receive the second vaccine on Day 22, the iSRC will meet on an ad hoc basis, to ensure there are no safety concerns and that none of the Individual Discontinuation Criteria or Study Halting Rules have been met, prior to the sentinel subjects receiving the second vaccine. When all subjects in Part A (18-49 years) low dose have received the first vaccination and have all safety data through Day 8, the iSRC will convene and review the safety data to ensure that there are no safety concerns and that none of the Study Halting Rules have been met before recommending that the study enroll Part A high dose and Part B low dose. The same strategy will be used for Part B when going from low to high dose. The iSRC will be asked to review unblinded immunogenicity and safety data when the first 30 subjects vaccinated in the Part A low dose group (including active and placebo subjects) have data available from Day 1 through Day 43 for an assessment of the risk-benefit of the trial. The iSRC will also meet when a minimum of 23 subjects have completed Day 29 after the second vaccination for Part A (low and high dose) and for Part B (low and high dose) to review safety data to ensure that there are no concerns. The iSRC will also review all data through Day 43 for Part A and for Part B in both dose groups to monitor for ongoing safety concerns and immunogenicity analysis. When the Parts A and B Day 43 (low and high dose) review is complete, the iSRC will recommend a dose for the Part C Expansion (optional). Progression to Part C will only take place after the Center for Biologics Evaluation and Research (CBER) has had the opportunity to review the Day 43 data from Parts A and B and concurs with the plan to proceed with enrollment. <u>Study Halting Rules:</u> The occurrence and confirmation of 1 or more of the following findings will result in suspension of further enrollment and study vaccine administration pending urgent review (within 1 week) of the safety data by the iSRC. Subjects who are withdrawn from study vaccine (if applicable) will continue to be monitored for safety and immunogenicity. • One or more subjects experience an SAE assessed as possibly related, probably related, or related to study vaccine without a plausible alternative explanation. • One or more subjects have generalized urticaria during the 7-day post vaccination period. • One or more subjects develop a Grade 4 local reaction for which there is no alternative plausible explanation. • One or more subjects experience laryngospasm, bronchospasm, or anaphylaxis after vaccine administration considered related to the vaccine. • One or more subjects develop a fever >40°C/104°F during the 7 days post vaccination period that is assessed as possibly related, probably related, or related to study vaccine without a plausible alternative explanation. • Two or more subjects within an individual treatment group, or 2 or more subjects across treatment groups, experience any Grade 3 or higher abnormality in the same laboratory parameter determined by the Investigator or medical monitor as clinically significant and that are assessed as possibly related, probably related, or related to study vaccine without a plausible alternative explanation. • Two or more subjects across treatment groups experience a Grade 3 or higher AE, MAAE, or AESI of the same or similar preferred terms (as categorized by the Medical Dictionary for Regulatory Activities [MedDRA]) assessed as possibly related, probably related, or related to study vaccine without a plausible alternative explanation. • Any subject with severe SARS-CoV-2 infection will be assessed for the possibility of vaccine-associated enhanced respiratory disease. Severe SARS-CoV-2 infection is defined as individuals who have virologically confirmed SARS-CoV-2 infection with any of the following: o Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 breaths per minute, heart rate ≥ 125 bpm, oxygen saturation (SpO_2) ≤ 93% on room

	air at sea level or partial pressure of oxygen/ fraction of inspired oxygen (PaO_2/FiO_2) < 300 mmHg) o Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation [ECMO]) o Evidence of shock (systolic blood pressure < 90 mmHg, diastolic blood pressure < 60 mmHg, or requiring vasopressors) o Significant acute renal, hepatic, or neurologic dysfunction o Admission to an intensive care unit (ICU) o Death due to SARS-CoV-2 infection The iSRC will review unblinded safety data for any subject who dies, requires ICU admission due to SARS-CoV-2 infection, develops an AESI of autoimmune disease or potential immune-medicated medical condition, or experiences vaccine-associated enhanced respiratory disease. If the subject had received TAP-COVID-19, the iSRC may decide whether a study halt for vaccine-enhanced disease is required based on a review of all available clinical and preclinical safety and immunogenicity data.
	<u>PART C EXPANSION (OPTIONAL):</u> The Part C Expansion may be conducted to confirm the safety and immunogenicity of a selected dose across the broad target age span using a larger sample size. The proposed sample size was selected based on World Health Organization (WHO) guidelines on clinical evaluation of vaccines: regulatory expectations Annex I (2001), which states that approximately 300 subjects are needed to identify common local reactogenicity events. A larger sample size will assist in a better characterization of kinetics and range of immunity (neutralizing antibody titers) and provide a more reliable output of seropositivity and seroconversion to TAP-COVID-19 immunization. With the limited clinical experience with SARS-CoV-2 vaccines and the current lack of a biomarker correlate of protection, the generation of this larger data set is relevant to inform the design and implementation of a Phase 3 program. After review of safety and immunogenicity data from Parts A and B through Day 43, a dose for the Phase II expansion study will be recommended by the iSRC. Progression to Part C will only take place after CBER has had the opportunity to review the human clinical plus additional nonclinical data and concurs with the plan to proceed with enrollment. Subjects ≥18 years of age will be enrolled and randomized 1:1 (selected active dose:placebo). Up to 1000 subjects will be enrolled at the chosen dose to provide expanded dose confirmation, safety, and immunogenicity data. Although all subjects in Part C will have safety laboratory tests performed at screening, only the first 200 subjects in Part C will have safety laboratory tests performed at all post-dose time points. The remaining subjects in Part C will not have safety laboratory tests performed at any of the post-dose time points unless the Investigator deems it necessary. Subjects who are seropositive for SARS-CoV-2 and asymptomatic will be allowed to enroll into Part C of the study.
Study Rationale:	Multiple vaccines have been approved for emergency use for the prevention of SARS-CoV-2, with other vaccines close to being available either through emergency use or licensed vaccines. Although work continues on antiviral treatments for SARS-CoV-2, given the crisis of COVID-19 infections in the world, the fast expansion to the United States and other parts of the world, and the global push to vaccinate everyone, additional sources of effective vaccine will be needed.
Subject Selection Criteria:	<u>Inclusion Criteria:</u> Subjects must meet all inclusion criteria to be eligible for study participation. In addition, racial and ethnic minorities will be sought to obtain a diverse study population. ***All Subjects*** 1. Subject read, understood, and signed the informed consent form (ICF). 2. Healthy adult males and females 18-49 years of age (Part A) or 50-85 years of age (Part B), inclusive, at screening.

	3. RT-PCR negative at time of screening 4. Body mass index (BMI) of ≥ 18 and ≤ 30 kg/m^2 at screening. BMI = weight (kg)/(height [m])^2. 5. Must be in general good health before study participation with no clinically relevant abnormalities that could interfere with study assessments. 6. Women of childbearing potential (WOCBP) and men whose sexual partners are WOCBP must be able and willing to use at least 1 highly effective method of contraception (ie, include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy, hormonal oral [in combination with male condoms with spermicide], transdermal, implant, or injection, barrier [ie, condom, diaphragm with spermicide]; intrauterine device; vasectomized partner [6 months minimum], clinically sterile partner; or abstinence) during the study. • A female subject is considered to be a WOCBP after menarche and until she is in a postmenopausal state for 12 consecutive months (without an alternative medical cause) or otherwise permanently sterile. • Note: Subjects not of childbearing potential are not required to use any other forms of contraception during the study. Non-childbearing potential is defined as subject confirmed: o Surgical sterilization (eg, bilateral oophorectomy, bilateral salpingectomy, bilateral occlusion by cautery [Essure System is not acceptable], hysterectomy, or tubal ligation). o Postmenopausal (defined as permanent cessation of menstruation for at least 12 consecutive months prior to screening) with follicle-stimulating hormone ≥ 30 mIU/mL at screening. 7. WOCBP must have a negative urine pregnancy test before each vaccination. 8. Must be able to attend all visits, including unscheduled visits if respiratory symptoms suggestive of SARS-CoV-2 infection develop during the study, for the duration of the study and comply with all study procedures, including daily completion of the Diary Card for 7 days after each injection. <u>Exclusion Criteria:</u> Subjects will not be eligible for study participation if they meet any of the exclusion criteria, or will be discontinued at the discretion of the Investigator if they develop any of the exclusion criteria during the study. ***Parts A and B*** 1. History of an acute or chronic medical condition including dementia that, in the opinion of the Investigator, would render vaccination unsafe or would interfere with the evaluation of responses. Chronic conditions that are NOT included on the Center for Disease Control's list of subjects at higher risk for severe illness from SARS-CoV-2 are acceptable if the condition has been stable for the 3 months prior to vaccine administration (Day 1), with no medication changes, and no hospitalization in the past 6 months. 2. History of any medical conditions that place subjects at higher risk for severe illness due to SARS-CoV-2 including but not limited to cancer, chronic kidney disease at any stage, chronic lung disease, dementia or other neurological conditions, diabetes (Type 1 or Type 2), Down syndrome, heart conditions, human immunodeficiency virus (HIV) infection, immunocompromised state (weakened immune system), liver disease, overweight/obesity, pregnancy, sickle cell disease or thalassemia, smoker (current or former), transplants (solid organ or blood stem cell), stroke or cerebrovascular disease, and substance use disorders. 3. History of ongoing clinical condition or medication or treatments that may adversely affect the immune system.

	4. Individuals who are RT-PCR positive for SARS-CoV-2 at screening or prior to second dose of TAP-COVID-19 vaccine. 5. Individuals who are at increased risk of exposure to SARS-CoV-2 (eg, healthcare workers, emergency responders). 6. Close contact of anyone known to have SARS-CoV-2 infection within 30 days prior to vaccine administration. 7. Living in a group care facility (eg, assisted living or nursing home). 8. Individuals with any elevated (Grade 1 or higher) laboratory test assessed as clinically significant for age by the Investigator at screening. 9. Individuals with elevated (Grade 1 or higher) liver function enzyme at screening, may repeat testing once to re-assess clinical significance. If the retest comes back within normal range, the subject will be eligible for enrollment with Investigator and Medical Monitor approval. See below for the criteria for excluding subjects with elevated liver enzymes (once confirmed by retest): • Alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), or gamma-glutamyl transferase (GGT) >1.5 × upper limit of normal (ULN) • Total bilirubin >1.6 × ULN 10. Active neoplastic disease (excluding nonmelanoma skin cancer that was successfully treated) or a history of any hematological malignancy. “Active” is defined as having received treatment within the past 5 years. 11. Long-term (greater than 2 weeks) use of oral or parenteral steroids, high-dose inhaled steroids (>800 µg/day of beclomethasone dipropionate or equivalent), or immunomodulatory drugs within 6 months before screening (nasal and topical steroids are allowed). 12. History of autoimmune, inflammatory disease, or potential immune-mediated medical conditions (Appendix B). 13. Women currently pregnant, lactating, or planning a pregnancy between enrollment and 181 days after randomization. 14. History of Guillain-Barré Syndrome. 15. History of anaphylactic-type reaction to injected vaccines. 16. Known or suspected hypersensitivity to 1 or more of the components of the vaccine, including thimerosal, tobacco, and CpG adjuvant. 17. History of alcohol abuse, illicit drug use, physical dependence to any opioid, or any history of drug abuse or addiction within 12 months of screening. Note: In those regions where cannabis use is legal, it will be left to the discretion of the Investigator to decide if a subject is an occasional user or an abuser of cannabis. The Investigator should discuss user/abuser status on a case-by-case basis with the Medical Monitor prior to enrollment. 18. Acute illness or fever within 3 days before study enrollment (enrollment may be delayed for full recovery if acceptable to the Investigator). 19. Individuals currently participating or planning to participate in a study that involves an experimental agent (vaccine, drug, biologic, device, or medication); or who have received an experimental agent within 1 month (3 months for immunoglobulins) before enrollment in this study; or who expect to receive another experimental agent during participation in this study. 20. Receipt of immunoglobulin or another blood product within the 3 months before enrollment in this study or those who expect to receive immunoglobulin or another blood product during this study. 21. Individuals who intend to donate blood within 6 months after the first vaccination. 22. Individuals using prescription medications for prophylaxis of SARS-CoV-2.

	23. Individuals who plan to receive another vaccine within the first 3 months of the study except influenza vaccine which should not be given within 2 weeks of study vaccine. 24. Receipt of any other approved SARS-CoV-2 vaccine prior to the first study vaccine or within 90 days after administration of the first study vaccine. 25. Receipt of any other experimental coronavirus vaccine at any time prior to or during the study. 26. Receipt of any investigational vaccine or drug within 1 month of enrollment and through the end of the study (1 year after first vaccination). 27. Plan to travel outside the subjects' country of residence from enrollment through Day 43. 28. History of surgery or major trauma within 12 weeks of screening, or surgery planned during the study. 29. Significant blood loss (>450 mL) or has donated 1 or more units of blood or plasma within 6 weeks prior to study participation. 30. Strenuous activity (as assessed by the Investigator) within 48 hours prior to dosing (Days 1 and 22). 31. A positive urine drug screen without evidence of corresponding prescribed concomitant medication(s) at Screening. Note: A positive drug screen result with a corresponding prescribed concomitant medication will be allowed if, in the opinion of the investigator and Medical Monitor, the concomitant medication does not make the subject unsuitable to participate in the clinical trial. For a positive tetrahydrocannabinol result, refer to Exclusion Criteria #17. 32. Positive alcohol screen. 33. Positive screen for HIV-1 and HIV-2 antibodies, hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV) antibody. 34. Involved in the planning or conduct of this study. 35. Unwilling or unlikely to comply with the requirements of the study. 36. Subject is an employee, contractor, friend of or relative of any employee of Sponsor, contract research organization (CRO), study site or site affiliate. ***Part C*** If the study proceeds to the Part C Expansion study, the following exclusion criteria (Number, from Parts A and B) will be not applicable. (5) Individuals who are at increased risk of exposure to SARS-CoV-2 (eg, healthcare workers, emergency responders). (6) Close contact of anyone known to have SARS-CoV-2 infection within 30 days prior to vaccine administration. (7) Living in a group care facility (eg, assisted living or nursing home). (31) A positive urine drug screen without evidence of corresponding prescribed concomitant medication(s) at Screening. Note: A positive drug screen result with a corresponding prescribed concomitant medication will be allowed if, in the opinion of the investigator and Medical Monitor, the concomitant medication does not make the subject unsuitable to participate in the clinical trial. (32) Positive alcohol screen. (33) Positive screen for HIV-1 and HIV-2 antibodies, HBsAg, or HCV antibody (Parts A and B). For Part C, subjects known to be HIV positive or have active Hepatitis B or C infection will be excluded.
Study Vaccine, Dose, and Route of Administration:	TAP-COVID-19: 0.5 mL of TAP-COVID-19 vaccine at 15 µg or 45 µg + CpG (0.5 mg), administered by IM injection on Day 1 and Day 22 (±3 days).

Reference Vaccine, Dose and Route of Administration:	Placebo: 0.5 mL buffered saline solution, administered by IM injection on Day 1 and Day 22 (±3 days).
Planned Sample Size:	No formal sample size calculation was performed. A total of 180 subjects will be enrolled in Parts A and B. Approximately 90 eligible subjects (aged 18-49 years), with 30 subjects per treatment group for Part A and 90 eligible subjects (aged 50-85 years), with 30 subjects per treatment for Part B, will be enrolled in the study. An optional Part C Expansion may be conducted to confirm the safety and immunogenicity of the selected dose of vaccine in up to 1000 adult subjects randomized 1:1 (single dose level of study vaccine:placebo). The proposed sample size was selected based on WHO guidelines on clinical evaluation of vaccines: regulatory expectations Annex I (2001), which states that approximately 300 subjects are needed to identify common local reactogenicity events. A larger sample size will assist in a better characterization of kinetics and range of immunity (neutralizing antibody titers) and provide a more reliable output of seropositivity and seroconversion to TAP-COVID-19 immunization. With the limited clinical experience with SARS-CoV-2 vaccines and the current lack of a biomarker correlate of protection, the generation of this larger data set is relevant to inform the design and implementation of a Phase 3 program.
Statistical Analysis:	Analysis Populations: Enrolled Population: All subjects who signed the ICF. Safety Population: All subjects who provided consent, are randomized, and received any amount of study vaccine/placebo. The Safety Population will be used for the demographic, baseline characteristic, safety data summaries, and the analysis of primary endpoints such as occurrence of solicited local and systemic reactogenicity. Per Protocol (PP) Population: Includes all subjects in the Safety Population who receive the assigned doses of the study vaccine/placebo according to protocol, have serology results, and have no major protocol deviations affecting the primary immunogenicity outcomes, as determined by the Sponsor before database lock and unblinding. Subjects that are immunized with an approved vaccine will be captured as a subset analysis of the PP Population at Days 90, 181, 273, and 365 based on the date of receiving an approved COVID-19 vaccine. Modified Intent-to-Treat (mITT) Population: Includes all subjects in the Safety Population who provide any serology data. The mITT Population will be used for immunogenicity analysis. Immunogenicity Analysis: The mITT Population will be used for all listings and summary statistics corresponding to immunogenicity analysis. The individual sampling and blood collection for ELISA analysis to determine IgG and IgM antibody titers to the spike RBD and neutralizing antibody titers for parent (Wuhan) and any variant SARS-CoV-2 strains, will be listed and summarized by time points for each part by treatment. All derived immunogenicity secondary endpoint parameters: GMT, GMT ratio, GMFR, GMI, and seroconversion rates will be listed and summarized by scheduled time point using descriptive statistics (n, mean, standard deviation, minimum, median, maximum, geometric mean, coefficient of variation (percentage) (CV%), geometric coefficient of variation (percentage) (GeoCV%), and 95% confidence interval) for each part by treatment. PBMC and serum sample data for future research results at each scheduled visit will also be provided separately in a listing and summary table, if applicable. Graphical display of the summary results or at individual time points will be provided as needed (eg, scatter plots of subject titer values to visually display individual data points).

	Cellular Analysis: The number of IFN-γ and IL-5 producing T-cells (CD4+ and CD8+) from PBMCs responsive to vaccine antigens will be listed and summarized by time point using appropriate descriptive statistics for each part by treatment. Safety Analysis: Safety Population will be used for all safety variables specified. All safety data will be summarized by part and treatment. No statistical tests will be performed. In addition, if any subjects seropositive for SARS-CoV-2 are enrolled, safety and efficacy subgroup analysis will be performed for this group of subjects.

1.1 Schedule of Assessments and Procedures

Table 1-1 Schedule of Assessments and Procedures

Study Visit	SCR	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13 Study End	UNSCH /ET
Study Day (Visit Window) / Procedures	Day -14 to Day -1	Day 1	Day 8 (±1 Day)	Day 15 (±1 Day)	Day 22 (±3 Days)	Day 29 (±2 Days)	Day 43 (±2 Days)	Day 76 (±3 Days)	Day 90 (±14 Days)	Day 120 (±3 Days)	Day 150 (±3 Days)	Day 181 (±14 Days)	Day 273 (±14 Days)	Day 365 (±14 Days)	
Informed consent	X														
Eligibility	X	X			X										
Medical history	X	X [a]	X [a]	X [a]	X [a]	X [a]	X [a]		X [a]			X [a]	X [a]	X [a]	X [a]
Demographic and baseline characteristics [b]	X														
Complete physical examination	X														
Targeted physical examination [c]		X	X	X	X	X	X					X			X
Height, weight, BMI	X														
Vital sign measurements [d]	X	X [d]	X	X	X [d]	X	X		X			X	X	X	X
Urine pregnancy test [e]	X	X			X										
Urine drug screen [f]	X														
HIV-1/2, HBsAg, HCV [g]	X														
Nasopharyngeal swab for RT-PCR [h]	X			X											X
Serostatus (IgM & IgG) for SARS-CoV-2 [q]	X														
Oral Temperature (pre-vaccination)		X			X										

Study Visit / Study Day (Visit Window) / Procedures	SCR Day -14 to Day -1	Visit 1 Day 1	Visit 2 Day 8 (±1 Day)	Visit 3 Day 15 (±1 Day)	Visit 4 Day 22 (±3 Days)	Visit 5 Day 29 (±2 Days)	Visit 6 Day 43 (±2 Days)	Visit 7 Day 76 (±3 Days)	Visit 8 Day 90 (±14 Days)	Visit 9 Day 120 (±3 Days)	Visit 10 Day 150 (±3 Days)	Visit 11 Day 181 (±14 Days)	Visit 12 Day 273 (±14 Days)	Visit 13 Study End Day 365 (±14 Days)	UNSCH /ET
Vaccination dose (IM)		X			X										
60 minute post-vaccination monitoring (arm check, VS, and targeted PE if general symptoms present)		X			X										
Distribution and training on Diary Card completion		X			X										
Review of Diary Card [i]			X			X									
Telephone visit [j]								X		X	X				
SARS-Cov-2 exposure and asymptomatic monitoring [k]	→	→	→	→	→	→	→	→	→	→	→	→	→	→	
Adverse events [l]		→	→	→	→	→	→								X
SAEs, MAAEs, NOCDs and AESIs [m]		→	→	→	→	→	→	→	→	→	→	→	→	→	X
Prior and concomitant medications [n]	→	→	→	→	→	→	→								X
Clinical safety laboratory tests [o]	X		X	X	X		X					X			X
Blood collection for ELISA IgM and IgG total antibodies [p]	X		X	X	X	X	X		X			X	X	X	X

Study Visit	SCR	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13 Study End	UNSCH /ET
Study Day (Visit Window) / Procedures	Day -14 to Day -1	Day 1	Day 8 (±1 Day)	Day 15 (±1 Day)	Day 22 (±3 Days)	Day 29 (±2 Days)	Day 43 (±2 Days)	Day 76 (±3 Days)	Day 90 (±14 Days)	Day 120 (±3 Days)	Day 150 (±3 Days)	Day 181 (±14 Days)	Day 273 (±14 Days)	Day 365 (±14 Days)	
Blood collection for neutralizing, anti-RBD, and anti-Fc antibodies	X		X	X	X	X	X		X			X	X	X	X
Cell-mediated immunity (PBMC)	X		X		X	X	X		X			X	X	X	X
PBMC and serum sample collection for future research	X		X		X	X	X		X			X	X	X	X

Abbreviations: AE = adverse event; AESI = adverse event of special interest; BMI = body mass index; CRU = clinical research unit; ELISA = enzyme-linked immunosorbent assay; ET = Early Termination visit; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; Ig = immunoglobulin; IM = intramuscular; MAAE = medically attended adverse event; NOCD = new-onset chronic disease; PBMC = peripheral blood mononuclear cells; PE = physical examination; RBD = receptor binding domain; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SCR = Screening visit; UNSCH = Unscheduled visit; VS = vital signs

a. Medical history will be collected to determine if any changes have occurred since last visit.

b. Baseline characteristics include tobacco use and history.

c. Post vaccination targeted physical examination includes evaluation of any system indicated by an AE complaint.

d. Pre-dose and approximately 60 minutes post vaccination. Vital signs will be measured after the subject has been resting quietly in a seated position for at least 5 minutes. Vital signs measurements will include blood pressure, heart rate, respiratory rate, and oral temperature.

e. A negative urine pregnancy test must be documented before vaccination on Day 1 and Day 22 for women of childbearing potential. A serum pregnancy test must be performed to confirm any positive urine pregnancy test.

f. For Parts A and B, a positive urine drug screen without evidence of corresponding prescribed concomitant medication(s) at Screening is exclusionary. A positive drug screen result with a corresponding prescribed concomitant medication will be allowed if, in the opinion of the Investigator and Medical Monitor, the concomitant medication does not make the subject unsuitable to participate in the clinical trial.

g. Not performed for Part C.

h. Serial nasopharyngeal swabs (RT-PCR) will be performed on subjects that report either potential exposure to SARS-CoV-2 (ie, close contact tests positive for SARS-CoV-2) or symptoms of SARS-CoV-2 infection. Testing will occur every 2 weeks for a total of 4 weeks (if 2 consecutive negative tests) or until negative after a positive result. Positive results will be reported as an AESI (Section 8.2.2) and subjects followed for disease severity, duration, and outcome.

i. Review of Diary Card (Appendix A) will include a check that the Diary Card has been completed appropriately and re-training the subjects, if necessary. Any illogical entries will be queried by the site and corrected if appropriate.

j. During telephone visits, CRU staff will interview the subjects about any potential exposure to the virus. If a subject has had potential exposure, the CRU will ask the subject to come in for an unscheduled visit which will include a nasopharyngeal swab. Subjects will be reminded to contact the clinical site any time there is potential exposure to SARS-CoV-2.

k. Subjects will be monitored for SARS-CoV-2 exposure for potential asymptomatic infection throughout the study. CRU staff will interview subjects about any potential exposure to the virus. If a subject has had potential exposure, the CRU will perform an unscheduled nasopharyngeal swab.

l. Adverse events include questioning regarding the specifically elicited events on the Diary Card and complaints spontaneously reported in response to nondirective questions.

m. SAEs, MAAEs, NOCDs, and AESIs will be collected from Day 1 through Day 365/approximately 1 year after first vaccination.

n. Includes all medications taken during the first 43 days of the study, including those started 30 days before and ongoing at vaccination.

o. Refer to Table 7-1 for a detailed list of clinical laboratory test parameters. Clinical laboratory tests can be repeated once at screening to confirm an out-of-range result. If Part C Expansion (optional) is performed, safety laboratory tests will be performed at screening for all Part C subjects in order to satisfy the inclusion/exclusion criteria. In addition, the first 200 subject in Part C will have safety laboratory tests performed at all time points. The remaining subjects in Part C will not have safety laboratory tests performed at any of the post-dose time points unless the Investigator deems it necessary.

p. Subjects with positive ELISA anti-N IgG results without COVID-19 symptoms may indicate asymptomatic SARS-CoV-2 infection and will be followed appropriately. Subjects with a positive ELISA anti-N IgG result should have a PCR test and be followed until both are negative as in the protocol instructions (Section 7.6).

q. Serostatus will not be used to determine eligibility; however, subjects with a positive serostatus for SARS-CoV-2 will have safety and efficacy subgroup analysis performed.

NOTE: In the event multiple post-dose procedures are required to be conducted at the same nominal time point, the timing of antibody titer and cellular immunity blood sample collections will take priority over all other scheduled activities. In practice, the following order is recommended: (1) vital signs measurements; (2) antibody titer and cellular immunity blood sampling; (3) clinical laboratory tests sampling; (4) physical examination and height and body weight measurements. Vital signs may be conducted up to 10 minutes, prior to the nominal time to minimize the potential autonomic effects of blood draws on these measurements and remaining assessments (eg, clinical laboratory tests sampling, physical examination, and height and body weight measurements) may be performed after the nominal time point.

TABLE OF CONTENTS

List of Tables

List of Figures

LIST OF ABBREVIATIONS

Abbreviation	Definition
ACE-2	angiotensin converting enzyme 2
ADE	antibody-mediated disease enhancement
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
BMI	body mass index
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CD4+	white blood cell T helper cell subtype
CD8+	white blood cell T cytotoxic cell subtype
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practice
CI	confidence interval
CoV	coronavirus
CpG	Cytosine PhosphoGuanine
CPMP	Committee for Proprietary Medicinal Products
CRA	clinical research associate
CRU	clinical research unit
CRO	contract research organization
CSR	clinical study report
CV%	coefficient of variation (percentage)
DAIDS	Division of AIDS
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
EOS	end-of-study
FcγRII	Fc gamma region II of IgG
FDA	Food and Drug Administration
FIH	first-in-human
FiO_2	fraction of inspired oxygen
FSH	follicle-stimulating hormone
GeoCV%	geometric coefficient of variation (percentage)
GGT	gamma-glutamyl transferase
GMFR	geometric mean fold rise
GMI	geometric mean increase
GMT	geometric mean titer
H1N1	influenza A virus subtype H1N1
H3N2	influenza A virus subtype H3N2

Abbreviation	Definition
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
ICD	International Classification of Diseases
ICF	informed consent form
ICU	intensive care unit
Ig	immunoglobulin
IL	interleukin
IM	intramuscular
IRB	institutional review board
IFN-γ	interferon gamma
iSRC	independent safety review committee
KBP	Kentucky BioProcessing, Inc.
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East Respiratory Syndrome coronavirus
mITT	Modified Intent-to-Treat Population
NOCD	new onset chronic disease
PaO_2	partial pressure of oxygen
PBMC	peripheral blood mononuclear cell
PE	physical examination
PP	Per Protocol
RBD	receptor binding domain
RBD-Fc	fusion protein containing RBD fused to the Fc domain of a human IgG1
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOP	standard operating procedure
SpO_2	oxygen saturation
SRM	study reference manual
SSP	study-specific procedure
TAP	Tobacco Mosaic Virus Antigen Presentation
TAP-COVID-19	Tobacco Mosaic Virus Antigen Presentation SARS-CoV-2 virus Receptor Binding Domain fused to Fc Domain
TEAE	treatment-emergent adverse event
TLR9	Toll-like Receptor 9
TMV	Tobacco Mosaic Virus
ULN	upper limit of normal
US or USA	United States of America
VS	vital signs
WHO	World Health Organization
WOCBP	Women of childbearing potential

STUDY ADMINISTRATIVE STRUCTURE

Sponsor:	Kentucky BioProcessing, Inc. 3700 Airpark Drive Owensboro, KY 42301 USA Telephone: 270-689-257
Sponsor's Contact:	Oscar (Tony) A. Guzman, MD, CP Clinical Project Lead Kentucky BioProcessing, Inc.
ICON Medical Monitor:	Bart Chapman, MD ICON Clinical Research, LLC 820 West Diamond Avenue, Suite 100 Gaithersburg, MD 20878 USA
ELISA (IgM & IgG) Antibody Titer and Cell Mediated Immunity Laboratories:	VisMederi srl Strada del Petriccio e Belriguardo, 35, 53100 Siena, Italia ICON Central Laboratory 123 Smith Street Farmingdale, NY 11735 USA
Neutralizing Antibody Laboratory:	VisMederi srl Strada del Petriccio e Belriguardo, 35, 53100 Siena, Italia
Clinical Research Organization:	ICON Clinical Research, LLC 820 West Diamond Avenue, Suite 100 Gaithersburg, MD 20878 USA Telephone: 301-944-6800

Multiple clinical sites may be utilized for Parts A and B. Multiple sites are also planned for Part C.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

To date, seven CoVs capable of human infection have been identified, including SARS-CoV, MERS-CoV, and a newly identified CoV (SARS-CoV-2). These 3 viruses, when in the human population, are significant public health risks showing high fatality rates: SARS-CoV = 10%, MERS-CoV = 34.4% and SARS-CoV-2 = 6.1%. The SARS-CoV-2 virus has spread to >180 countries since December 2019, infected >5.7 million humans, and been attributed to >350,000 deaths worldwide [John Hopkins 2020]. These numbers are growing exponentially, creating worldwide health and economic crises. The emergence of this disease and its effects on human health and economic security demands urgent response.

TAP-COVID-19 Vaccine is being developed for the prevention of SARS-CoV-2 infection in healthy adults aged 18 and older. For this Phase 1 Study, the TAP-COVID-19 vaccine will be evaluated with a CpG adjuvant based on preclinical studies showing it provides a Th1 biased immune response against SARS-CoV-2.

2.2 Study Vaccine Background

2.2.1 Receptor Binding Domain Vaccine Strategy

Focusing CoV vaccine efforts around the RBD (S1 domain) of the spike glycoprotein have produced encouraging outcomes. SARS-CoV RBD has been shown to bind the human receptor for ACE-2, contains multiple conformation-dependent epitopes that can elicit high-titer neutralizing antibodies [Wang 2020; Kam 2007; Jaume 2012; Quinlan 2020]. Most relevant to the KBP vaccine strategy, in vivo studies showed that a fusion protein containing RBD-Fc elicited high levels of neutralizing antibodies against SARS-CoV in both immunized rabbits and mice. These antibodies blocked spike interaction with the human receptor ACE-2. Most interestingly, the RBD-Fc protein induced long lasting, potent neutralizing antibody titers maintained for 12 months after immunization – even protecting most vaccinated mice from SARS-CoV challenge [Du 2007; Du 2009]. Importantly, many different versions of SARS or MERS-RBD vaccines have been developed and tested, alone and with adjuvant, produced in mammalian cells, and insect cells and plants. All have shown protection from infection through virus neutralization without accompanying immunopathology associated with full-length or trimerized S protein vaccines [Wang 2020; Kam 2007; Jaume 2012; Quinlan 2020].

2.2.2 TAP-COVID-19 Vaccine – A Novel Vaccine for COVID-19 Disease Prevention

Based on the prior experience with Coronavirus family viruses described above, KBP has developed the RBD-Fc antigen linked to its novel TAP platform to accelerate development of an effective and scalable vaccination strategy. The KBP platform combines the well-established speed and robustness of its transient Nicotiana benthamiana gene expression system with the immune stimulation effects of antigen-association with the inactivated TMV virus structure. Using standardized gene expression and downstream processing strategies, while maintaining a warm

base of naïve plants, the TAP platform has the potential to rapidly deliver vaccines with significant production potential of millions of doses of vaccine API per month.

Historical preclinical data illustrates the ability of TAP vaccines to provide balanced humoral and cellular responses in mammals allowing efficacious responses to be generated against a wide range of pathogens with different immune correlates of protection [McCormick 2006a; McCormick 2006b; Banik 2015; Arnaboldi 2016; Mallajosyula 2016; Mallajosyula 2014].

The TAP vaccine system offers key advantages of:

- Speed: <10 weeks from sequence to cGMP vaccine
- Balanced immune response: effective stimulation of both Th1 and Th2 arms of the immune system
- Stability: showing room temperature shelf life past 6-months at room temperature with no loss of potency
- Scalability: potential to deliver millions of doses of vaccine API per month
- Robustness: showing safety in murine, ferret, and rabbit preclinical models and efficacy against challenge with seven viruses and three bacterial pathogens, including human influenza virus, Yersinia pestis, Francisella tularensis, and Mycobacterium tuberculosis

2.2.3 CpG Adjuvant

The TAP-COVID-19 Vaccine will be combined with CpG 7909 adjuvant. CpG 7909 is a short (24 nucleotide) synthetic form of DNA that mimics bacterial and viral genetic material that, when included into a vaccine, increases the body's immune response through engagement of TLR9 within antigen presenting dendritic cells and B cells. TLR9-engaging adjuvants are known to generate Th1 cell- and cytokine-mediated immune responses (IFN-γ and IL-2) generated by Th1 cells and IgG2a isotype antibodies and to vaccine antigens and pathogens. Generation of a Th1-biased humoral response may reduce risk associated with antibody-mediated disease enhancement based on FcγRII receptor affinity for Th1 antibodies versus Th2 antibodies [de Alwis 2020; Fierz 2020].

2.2.4 Data Supporting Development of TAP-COVID-19 Vaccine

2.2.4.1 Binding to CR3022 Monoclonal Antibodies

Preliminary data indicates the RBD-Fc intact antigen binds to the human ACE-2 receptor and a SARS-CoV-2 RBD-specific, human neutralizing monoclonal antibody, CR3022. The data shows strong, dose-dependent binding of CR3022 to RBD-Fc antigen and RBD-Fc TAP vaccine. The RBD-Fc candidate antigens show >5X reactivity to CR3022 compared with commercially sourced control SARS spike and RBD reagents. These data suggest that the purified SARS-CoV-2 RBD-Fc antigen maintains essential conformational epitopes in a manner superior to commercially purchased reagents.

2.2.4.2 Binding to ACE-2 Receptor

Recombinant ACE-2 complexes containing RBD-Fc can be immunoprecipitated by ACE-2 specific antisera in vitro. However, this does not provide a quantitative measure of binding. Quantitative and functional ACE-2 binding was performed using confocal microscopy and analysis by co-localization and competitive binding methods on Vero e6 cells in collaboration with scientists at the University of Louisville, Center for Predictive Medicine and Department of Microbiology & Immunology. The ability of the native agonist, angiotensin II, was compared with the RBD-Fc fusion or concentration dependent ability to block binding of an ACE-2 specific antibody to the receptor on living cells. Influenza H7 hemagglutinin was used as a control. FAM-angiotensin II bound to Vero e6 cells, with an average of a 2.79-fold increase over the non-specific H7 control.

Binding of the RBD-Fc antigen to Vero e6 cells occurred in a concentration-dependent manner with an increase of 2.58-fold increase over the H7 control. Binding of H7 did not impact detection of ACE-2 by monoclonal antibody at any concentration.

SARS-CoV-2 RBD-Fc fusion antigen shows functional conformation and activity through the binding by CR3022 and ACE-2. Binding to ACE-2 shows similar affinity and specificity as angiotensin II suggesting that the conformation of the spike protein RBD in the antigen-antibody complex is comparable to that observed with native SARS-CoV-2 spike protein. The data suggests that both antigen-antibody complexes display the correct structure necessary to elicit neutralizing antibodies to the RBD of SARS-CoV-2 spike protein.

2.3 Summary of Findings to Date

KBP is also actively developing a quadrivalent seasonal influenza vaccine, TAP-V001, using the TAP platform. Nonclinical studies performed to support TAP-V001 are relevant and supportive of the TAP-COVID-19 program based on the quantities of the vaccine components. In particular, IND-enabling pharmacokinetic/biodistribution and GLP repeat dose toxicology studies have been completed using two different formulations of TAP-V001 vaccine that demonstrated:

- No observed treatment-related or toxicologically significant clinical findings or inoculation site reactogenicity
- No observed treatment-related or toxicologically significant effects for body weights, body weight changes, food consumption, body temperatures, ophthalmology, clinical chemistry, hematology, organ weights, and gross and microscopic pathology
- Dose dependent TMV-specific RT-PCR signal measured at site of injection with rapid clearance from all non-target organs
- Maintenance of TMV-specific RT-PCR signal in immune-processing organs, including lymph nodes and spleen
- Efficacy in two ferret challenge studies, revealing statistically improved H1N1 clearance and statistically equivalent H3N2 clearance compared with Fluzone® control.

The same platform manufacturing process for production of TAP-V001 is used in the production of TAP-COVID-19, with the exception of the affinity chromatography resin, and a similar drug product formulation is employed.

2.4 Study Rationale

Multiple vaccines have been approved for emergency use for the prevention of SARS-CoV-2, with other vaccines close to being available either through emergency use or licensed vaccines. Although work continues on antiviral treatments for SARS-CoV-2, given the crisis of COVID-19 infections in the world, the fast expansion to the US and other parts of the world, and the global push to vaccinate everyone, additional sources of effective vaccine will be needed.

2.5 Dose Rationale

As SARS-CoV-2 is a newly emergent respiratory viral disease, naïve subjects are expected to require a two dose (prime-boost) immunization regimen to generate a suitable immune response to offer protection from infection. The TAP-COVID-19 vaccine dose levels to be evaluated have been established using a prime-boost dosing strategy in mice as a model species to characterize the vaccine's immunogenicity. Two doses of TAP-COVID-19 have demonstrated a robust and dose-dependent increase in the humoral antibody response to the vaccine in both total antibody and neutralizing antibody titers. This response was seen in separate KBP studies conducted at two different academic centers.

The selected regimen is anticipated to be safe based on nonclinical toxicology studies conducted in rabbits which employed a 4-fold higher antigenic dose levels of a quadrivalent influenza vaccine candidate. There were no toxicologically relevant findings and it was determined that a property of TAP-based vaccines is the trafficking to immune organs (draining lymph nodes and spleen) which may serve as a mechanism for driving the immune response.

Lastly, the proposed rationale for dose level and the dosing regimen is based on historical experience with other pandemic respiratory viral diseases including influenza and prior coronavirus outbreaks and is also consistent with other ongoing SARS-CoV-2 clinical studies.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives

3.1.1 Primary Objective

To assess the safety and reactogenicity of two doses of TAP-COVID-19 vaccine with CpG adjuvant for 7 days post vaccination compared with placebo as determined by solicited local and systemic reactogenicity

3.1.2 Secondary Objectives

To compare the frequency of unsolicited AEs of each dose of TAP-COVID-19 vaccine with CpG adjuvant through Day 43 and SAEs, MAAEs, NOCDs, and AESIs through Day 365

Comparisons include:

- High dose (45 μg TAP-COVID-19 vaccine + 0.5 mg CpG) to placebo
- Low dose (15 μg TAP-COVID-19 vaccine + 0.5 mg CpG) to placebo
- High dose (45 μg TAP-COVID-19 vaccine + 0.5 mg CpG) to low dose (15 μg TAP-COVID-19 vaccine + 0.5 mg CpG)

To evaluate the immunogenicity of TAP-COVID-19 vaccine with CpG adjuvant compared with placebo in terms of antibody assessed by GMTs of both spike RBD IgG and IgM antibodies and neutralizing antibody response, GMFR in neutralizing titer from baseline in all treatment groups at Days 8, 22, 29, 43, 90, 181, 273, and 365 relative to baseline

3.1.3 Exploratory Objectives

To assess cellular immunity by measuring the numbers of cytokine producing CD4+ and CD8+ T-cells from PBMCs response to vaccine in all treatment groups at Days 8, 22, 29, 43, 90, 181, 273, and 365 compared to baseline

To assess the immunogenicity of the RBD and Fc component of the vaccine

3.2 Endpoints

3.2.1 Primary Endpoints

Occurrence of Solicited AEs:

- Solicited administration site reactions (eg, pain, tenderness, erythema/redness, induration/swelling) during the 7-day follow-up period after each vaccination (Day 1-8 and Day 22-29)

- Solicited systemic events (eg, fever, nausea/vomiting, diarrhea, headache, fatigue, myalgia) during the 7-day follow-up period after each vaccination (Day 1-8 and Day 22-29)

3.2.2 Secondary Endpoints

Safety:

- Unsolicited AEs, MAAEs, and AESIs up to Day 43
- SAEs, MAAEs, NOCDs, and AESIs up to Day 365 (approximately 1 year after first vaccination)

Immunogenicity:

- Vaccine ELISA of both RBD IgG and IgM antibodies and neutralizing antibody titers for each treatment group:
  - GMT at baseline and Days 15, 22, 43, 90, 181, 273, and 365
  - GMT ratio ($GMT_{placebo}/GMT_{TAP\text{-}COVID\text{-}19}$) at baseline and Days 22, 29, 43, 90, 181, 273, and 365
  - GMFR at Days 8, 22, 29, 43, 90, 181, 273, and 365 relative to baseline
  - Seroconversion rates on Days 8, 15, 22, 29, 43, 90, 181, 273, and 365. Seroconversion is defined as the proportion of subjects at the respective time point that have detectable antibodies (IgG and IgM) against SARS-CoV-2 Spike Protein RBD following challenge with vaccine (and potentially by natural asymptomatic or symptomatic infection by the virus in case of a placebo subject).
  - GMI on Days 8, 22, 29, 43, 90, 181, 273, and 365

3.2.3 Exploratory Endpoints

Cellular immunity:

- The number of cytokine producing CD4+ and CD8+ T-cells from PBMCs responsive to vaccine antigens in all treatment groups on Days 8, 22, 29, 43, 90, 181, 273, and 365 compared to baseline

Immunogenicity:

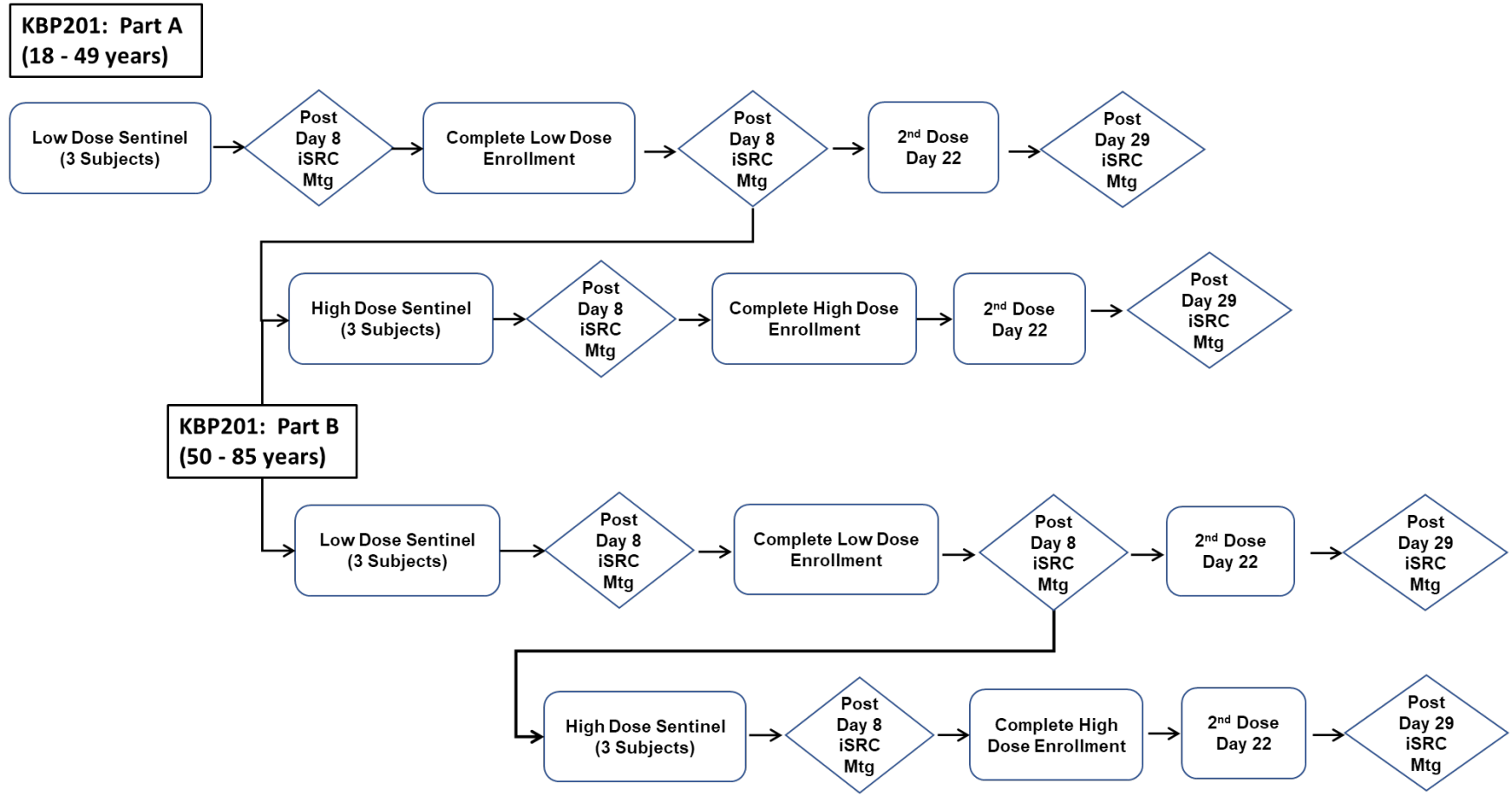
- Anti-RBD and anti-Fc antibodies at baseline and Days 8, 15, 22, 29, 43, 90, 181, 273, and 365

4 STUDY DESIGN

4.1 Study Design and Overview

This is an FIH, observer-blinded, randomized, placebo-controlled, parallel group study to evaluate the safety and immunogenicity of TAP-COVID-19 vaccine with CpG adjuvant in healthy adult subjects in 2 age groups, Part A (18-49 years) and Part B (50-85 years). A study schematic is presented in Figure 4-1.

Figure 4-1 Study Schematic for Parts A and B



Abbreviations: High Dose = 45 µg TAP-COVID-19 vaccine + CpG (0.5 mg); iSRC = independent Safety Review Committee; Low Dose = 15 µg TAP-COVID-19 vaccine+ CpG (0.5 mg); Mtg = meeting

Part A and Part B:

Subjects will be screened up to 14 days (Day -14 to Day -1) before randomization. Overall, approximately 90 eligible healthy adults ages 18-49 years (inclusive) will be enrolled for Part A and 90 eligible healthy adults ages 50-85 years will be enrolled for Part B.

Sentinel dosing will be utilized in this FIH study. Sentinel cohorts will be used for the following groups:

- Part A (18-49 years) low dose (15 µg TAP-COVID-19 vaccine + 0.5 mg CpG)
- Part B (50-85 years) low dose (15 µg TAP-COVID-19 vaccine + 0.5 mg CpG)
- Part A (18-49 years) high dose (45 µg TAP-COVID-19 vaccine + 0.5 mg CpG)
- Part B (50-85 years) high dose (45 µg TAP-COVID-19 vaccine + 0.5 mg CpG)

Three sentinel subjects from each part will be randomized 2:1 (active:placebo). The iSRC will review the safety data for the sentinel subjects through Day 8 prior to enrollment of the remaining cohort subjects randomized 2:1 (active:placebo). In the event that iSRC has not met for the post Day 8 review because the entire sentinel group (n = 3) has not completed Day 8 before a sentinel subject is to receive the second vaccine on Day 22, the iSRC will meet on an ad hoc basis, to ensure there are no safety concerns and that none of the Individual Discontinuation Criteria (Section 5.5) or Study Halting Rules (Section 5.7.2) have been met, prior to the sentinel subjects receiving the second vaccine.

When all subjects in Part A (18-49 years) low dose have received the first vaccination and have all safety data through Day 8, the iSRC (Section 5.7.1) will convene and review the safety data to ensure that there are no safety concerns and that none of the Study Halting Rules have been met (Section 5.7.2) before recommending that the study enroll Part A high dose and Part B (50-85 years) low dose.

When all subjects in Part B (50-85 years) low dose have received the first vaccination and have all safety data through Day 8, the iSRC will convene and review the safety data to ensure that there are no safety concerns and that none of the Study Halting Rules have been met before recommending that the study enroll Part B high dose.

The iSRC will convene and review the safety data when a minimum of 23 subjects have completed Day 29 after the second vaccination for Part A (low and high dose) and for Part B (low and high dose) to ensure that there are no concerns.

Both Part A (18-49 years) and Part B (50-85 years) will be randomized in a 2:1 ratio (active:placebo) for each treatment dose (15 µg and 45 µg TAP-COVID-19 vaccine + 0.5 mg CpG) for a total of 90 subjects per Part (30 subjects 15 µg TAP-COVID-19 vaccine + 0.5 mg CpG:30 subjects 45 µg TAP-COVID-19 vaccine + 0.5 mg CpG:30 subjects placebo).

Treatment A: TAP-COVID-19 vaccine (15 µg) + CpG (0.5 mg) IM injection on Day 1 and Day 22 (±3 days)

Treatment B: TAP-COVID-19 vaccine (45 µg) + CpG (0.5 mg) IM injection on Day 1 and Day 22 (±3 days)

Treatment C: Placebo (buffered saline solution) IM injection on Day 1 and Day 22 (±3 days)

Study vaccine will be prepared by an unblinded site pharmacist and administered at the clinical research site on Day 1 and Day 22 (±3 days) by unblinded CRU personnel. Subjects will be observed for immediate AEs and/or reactogenicity for approximately 60 minutes after administration of vaccine. Subjects will be provided with a Diary Card and will be trained to record specifically elicited systemic and local symptoms daily as well as any additional AEs during the 7-day follow-up period after each vaccination. Visits will be conducted at the clinical site on an outpatient basis or as a telephone visit per the Schedule of Assessments and Procedures (Table 1-1). Subjects will participate in the study for approximately 1 year from the first dose.

AEs and concomitant medications will be captured through Day 43. Blood and serum samples for safety laboratory tests, RBD IgG and IgM antibodies, and neutralizing antibody titers, cell-mediated immunity, and other future biomedical research will be obtained at baseline and before administration of vaccine dose 2 and after each vaccination per the Schedule of Assessments and Procedures (Table 1-1). SAEs, MAAEs, NOCDs, and AESIs only will be captured after Day 43 to study completion (Day 365 [approximately 1 year after vaccination]).

Prior to receiving a second dose of vaccine, subjects will have the following assessments performed to ensure eligibility: vital signs (including temperature), review of clinical laboratory test results to date, nasopharyngeal swab Day 15 to check for SARS-CoV-2 infection (RT-PCR result must be received by the CRU and negative prior to the second vaccine administration), medical history since last visit including AE assessment for SAEs, Grade 3 AEs, or AESIs that are possibly, probably, or definitely related to study vaccine without a plausible alternative explanation, targeted physical examination, recheck of eligibility criteria, and pregnancy test (as applicable).

Subjects will be monitored for SARS-CoV-2 exposure for potential asymptomatic infection throughout the study.

- If a subject has a positive or borderline ELISA anti-N IgG result, sites should have the subject return for an unscheduled PCR. If the ELISA is positive and the PCR is negative, the sites should follow the subjects using the standard of care under Investigator discretion, retesting ELISA at the next study visit(s) or sooner (per the Investigator's decision).

- If the subject has a positive or borderline ELISA anti-N IgG AND a positive PCR test, the clinical sites should bring the subjects back for repeat PCR testing as described below.

- The clinical sites should continue to collect PCR tests if a subject is experiencing possible COVID-19 symptoms, or had possible exposure to SARS-CoV-2 (ie, close contact tests positive for SARS-CoV-2). Testing will occur every 2 weeks for a total of 4 weeks (if 2 consecutive negative tests) or until negative (x2) after a positive result. Positive results

will be reported as an AESI (Section 8.2.2) and subjects followed for disease severity, duration, and outcome.

Subjects who are seropositive for SARS-CoV-2 and asymptomatic will be allowed to enroll into Parts A and B of the study as long as the subject is RT-PCR negative.

Additional details for the ELISA test results are presented in Appendix C.

Part C Expansion (Optional):

The Part C Expansion may be conducted to confirm the safety and immunogenicity of a selected dose across the broad target age span using a larger sample size. The proposed sample size was selected based on WHO guidelines on clinical evaluation of vaccines: regulatory expectations Annex I (2001), which states that approximately 300 subjects are needed to identify common local reactogenicity events. A larger sample size will assist in a better characterization of kinetics and range of immunity (neutralizing antibody titers) and provide a more reliable output of seropositivity and seroconversion to TAP-COVID-19 immunization. With the limited clinical experience with SARS-CoV-2 vaccines and the current lack of a biomarker correlate of protection, the generation of this larger data set is relevant to inform the design and implementation of a Phase 3 program. After review of safety and immunogenicity data from Parts A and B through Day 43, a dose for the Phase II expansion study will be recommended by the iSRC. Progression to Part C will only take place after CBER has had the opportunity to review the human clinical plus additional nonclinical data and concurs with the plan to proceed with enrollment. Subjects ≥18 years of age will be enrolled and randomized 1:1 (selected active dose:placebo). Up to 1000 subjects will be enrolled at the chosen dose to provide expanded dose confirmation, safety, and immunogenicity data. Although all subjects in Part C will have safety laboratory tests performed at screening, only the first 200 subjects in Part C will have safety laboratory tests performed at all post-dose time points. The remaining subjects in Part C will not have safety laboratory tests performed at any of the post-dose time points unless the Investigator deems it necessary.

Subjects who are seropositive for SARS-CoV-2 and asymptomatic will be allowed to enroll into Part C of the study.

4.1.1 Duration of Study

Each subject will receive two doses of study vaccine or placebo, the first on Day 1 and the second on Day 22 (±3 days). The total duration of subject participation is approximately 1 year (including screening, treatment, and follow-up periods).

4.1.2 Interim Safety Data Review

For all of the sentinel groups, the iSRC will meet to review the sentinel subjects' safety and tolerability data through Day 8. In the event that iSRC has not met for the post Day 8 review because the entire sentinel group (n = 3) has not completed Day 8 before a sentinel subject is to receive the second vaccine on Day 22, the iSRC will meet on an ad hoc basis, to ensure there are no safety concerns and that none of the Individual Discontinuation Criteria (Section 5.5) or Study

Halting Rules (Section 5.7.2) have been met, prior to the sentinel subjects receiving the second vaccine.

When all subjects in Part A (18-49 years) low dose have received the first vaccination and have all safety data through Day 8, the iSRC (Section 5.7.1) will convene and review the safety data to ensure that there are no safety concerns and that none of the Study Halting Rules have been met (Section 5.7.2) before recommending that the study enroll Part A high dose and Part B low dose. The same strategy will be used for Part B when going from low to high dose.

The iSRC will be asked to review unblinded immunogenicity and safety data when the first 30 subjects vaccinated in the Part A low dose group (including active and placebo subjects) have data available from Day 1 through Day 43 for an assessment of the risk-benefit of the trial. For the interim analysis, treatment codes will be unblinded and only after the data are deemed ready for the analysis and the data has been monitored. The unblinded review will be completed by the iSRC only and the other team members (CRO [except for the unblinded team members preparing the data for unblinded iSRC review], Investigator, and site personnel) will remain blinded until completion of the study. The Sponsor will be unblinded at the interim analysis.

The iSRC will also meet when a minimum of 23 subjects have completed Day 29 after the second vaccination for Part A (low and high dose) and for Part B (low and high dose) to review safety data to ensure that there are no concerns.

The iSRC will also review all data through Day 43 for Part A and for Part B in both dose groups to monitor for ongoing safety concerns and immunogenicity analysis. When the Parts A and B Day 43 (low and high dose) review is complete, the iSRC will recommend a dose for the Part C Expansion (optional). Progression to Part C will only take place after CBER has had the opportunity to review the Day 43 data from Parts A and B and concurs with the plan to proceed with enrollment.

4.1.3 Definition of Study Completion

End-of-study procedures will be performed as specified in the Schedule of Assessments and Procedures (Table 1-1); subjects who withdraw from the study early will have EOS procedures performed at the time of discontinuation. If a subject refuses to return for the EOS blood samples, the safety follow-up will be completed via telephone. Subjects with ongoing clinically significant clinical or laboratory findings will be followed until the finding is resolved or medically stable; reasonable attempts will be made to follow-up with subjects. The subject's participation in the study will end once all study assessments and follow-up have been completed.

4.1.4 End of Study

The end of the study is defined as the date when the last subject has completed all study procedures up to and including the EOS/early termination visit as specified in the Schedule of Assessments and Procedures (Table 1-1).

5 SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Inclusion Criteria

Subjects must meet all inclusion criteria to be eligible for study participation. In addition, racial and ethnic minorities will be sought to obtain a diverse study population.

All Subjects

1. Subject read, understood, and signed the ICF.
2. Healthy adult males and females 18-49 years of age (Part A) or 50-85 years of age (Part B), inclusive, at screening.
3. RT-PCR negative at time of screening.
4. BMI of $\geq$ 18 and $\leq$ 30 kg/m^2 (National Heart, Lung, and Blood Institute) at screening. BMI = weight (kg)/(height [m])^2.
5. Must be in general good health before study participation with no clinically relevant abnormalities that could interfere with study assessments.
6. WOCBP and men whose sexual partners are WOCBP must be able and willing to use at least 1 highly effective method of contraception (ie, include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy, hormonal oral [in combination with male condoms with spermicide], transdermal, implant, or injection, barrier [ie, condom, diaphragm with spermicide]; intrauterine device; vasectomized partner [6 months minimum], clinically sterile partner; or abstinence) during the study.
    - A female subject is considered to be a WOCBP after menarche and until she is in a postmenopausal state for 12 consecutive months (without an alternative medical cause) or otherwise permanently sterile.
    - Note: Subjects not of childbearing potential are not required to use any other forms of contraception during the study. Non-childbearing potential is defined as subject confirmed:
        - Surgical sterilization (eg, bilateral oophorectomy, bilateral salpingectomy, bilateral occlusion by cautery [Essure System is not acceptable], hysterectomy, or tubal ligation)
        - Postmenopausal (defined as permanent cessation of menstruation for at least 12 consecutive months prior to screening) with FSH $\geq$ 30 mIU/mL at screening
7. WOCBP must have a negative urine pregnancy test before each vaccination.
8. Must be able to attend all visits, including unscheduled visits if respiratory symptoms suggestive of SARS-CoV-2 infection develop during the study, for the duration of the study and comply with all study procedures, including daily completion of the Diary Card for 7 days after each injection.

5.2 Exclusion Criteria

Subjects will not be eligible for study participation if they meet any of the exclusion criteria, or will be discontinued at the discretion of the Investigator if they develop any of the exclusion criteria during the study.

Parts A and B

1. History of an acute or chronic medical condition including dementia that, in the opinion of the Investigator, would render vaccination unsafe or would interfere with the evaluation of responses. Chronic conditions that are NOT included on the CDC's list of subjects at higher risk for severe illness from SARS-CoV-2 (CDC COVID-19 website) are acceptable if the condition has been stable for the 3 months prior to vaccine administration (Day 1), with no medication changes, and no hospitalization in the past 6 months.
2. History of any medical conditions that place subjects at higher risk for severe illness due to SARS-CoV-2 including but not limited to cancer, chronic kidney disease at any stage, chronic lung disease, dementia or other neurological conditions, diabetes (Type 1 or Type 2), Down syndrome, heart conditions, HIV infection, immunocompromised state (weakened immune system), liver disease, overweight/obesity, pregnancy, sickle cell disease or thalassemia, smoker (current or former), transplants (solid organ or blood stem cell), stroke or cerebrovascular disease, and substance use disorders. (See the latest updates at the CDC COVID-19 website.)
3. History of ongoing clinical condition or medication or treatments that may adversely affect the immune system.
4. Individuals who are RT-PCR positive for SARS-CoV-2 at screening or prior to second dose of TAP-COVID-19 vaccine.
5. Individuals who are at increased risk of exposure to SARS-CoV-2 (eg, healthcare workers, emergency responders).
6. Close contact of anyone known to have SARS-CoV-2 infection within 30 days prior to vaccine administration.
7. Living in a group care facility (eg, assisted living or nursing home).
8. Individuals with any elevated (Grade 1 or higher) laboratory test assessed as clinically significant for age by the Investigator at screening (Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007), Tables for Laboratory Abnormalities).
9. Individuals with elevated (Grade 1 or higher) liver function enzyme at screening, may repeat testing once to re-assess clinical significance. If the retest comes back within normal range, the subject will be eligible for enrollment with Investigator and Medical Monitor approval. See below for the criteria for excluding subjects with elevated liver enzymes (once confirmed by retest):
    - ALP, ALT, AST, or GGT >1.5 × ULN
    - Total bilirubin >1.6 × ULN

10. Active neoplastic disease (excluding nonmelanoma skin cancer that was successfully treated) or a history of any hematological malignancy. "Active" is defined as having received treatment within the past 5 years.
11. Long-term (greater than 2 weeks) use of oral or parenteral steroids, high-dose inhaled steroids (>800 µg/day of beclomethasone dipropionate or equivalent), or immunomodulatory drugs within 6 months before screening (nasal and topical steroids are allowed).
12. History of autoimmune, inflammatory disease, or potential immune-mediated medical conditions (Appendix B).
13. Women currently pregnant, lactating, or planning a pregnancy between enrollment and 181 days after randomization.
14. History of Guillain-Barré Syndrome.
15. History of anaphylactic-type reaction to injected vaccines.
16. Known or suspected hypersensitivity to 1 or more of the components of the vaccine, including thimerosal, tobacco, and CpG adjuvant.
17. History of alcohol abuse, illicit drug use, physical dependence to any opioid, or any history of drug abuse or addiction within 12 months of screening.

    Note: In those regions where cannabis use is legal, it will be left to the discretion of the Investigator to decide if a subject is an occasional user or an abuser of cannabis. The Investigator should discuss user/abuser status on a case-by-case basis with the Medical Monitor prior to enrollment.
18. Acute illness or fever within 3 days before study enrollment (enrollment may be delayed for full recovery if acceptable to the Investigator).
19. Individuals currently participating or planning to participate in a study that involves an experimental agent (vaccine, drug, biologic, device, or medication); or who have received an experimental agent within 1 month (3 months for immunoglobulins) before enrollment in this study; or who expect to receive another experimental agent during participation in this study.
20. Receipt of immunoglobulin or another blood product within the 3 months before enrollment in this study or those who expect to receive immunoglobulin or another blood product during this study.
21. Individuals who intend to donate blood within 6 months after the first vaccination.
22. Individuals using prescription medications for prophylaxis of SARS-CoV-2.
23. Individuals who plan to receive another vaccine within the first 3 months of the study except influenza vaccine which should not be given within 2 weeks of study vaccine.
24. Receipt of any other approved SARS-CoV-2 vaccine prior to the first study vaccine or within 90 days after administration of the first study vaccine.
25. Receipt of any other experimental coronavirus vaccine at any time prior to or during the study.
26. Receipt of any investigational vaccine or drug within 1 month of enrollment and through the end of the study (1 year after first vaccination).

27. Plan to travel outside the subjects' country of residence from enrollment through Day 43.
28. History of surgery or major trauma within 12 weeks of screening, or surgery planned during the study.
29. Significant blood loss (>450 mL) or has donated 1 or more units of blood or plasma within 6 weeks prior to study participation.
30. Strenuous activity (as assessed by the Investigator) within 48 hours prior to dosing (Days 1 and 22).
31. A positive urine drug screen without evidence of corresponding prescribed concomitant medication(s) at Screening. Note: A positive drug screen result with a corresponding prescribed concomitant medication will be allowed if, in the opinion of the investigator and Medical Monitor, the concomitant medication does not make the subject unsuitable to participate in the clinical trial. For a positive tetrahydrocannabinol result, refer to Exclusion Criteria #17.
32. Positive alcohol screen.
33. Positive screen for HIV-1 and HIV-2 antibodies, HBsAg, or HCV antibody.
34. Involved in the planning or conduct of this study.
35. Unwilling or unlikely to comply with the requirements of the study.
36. Subject is an employee, contractor, friend of or relative of any employee of Sponsor, CRO, study site or site affiliate.

Part C

If the study proceeds to the Part C Expansion study to confirm the safety and immunogenicity of the selected dose of vaccine, the following exclusion criteria (Number, from Parts A and B above) will be not applicable.

(5) Individuals who are at increased risk of exposure to SARS-CoV-2 (eg, healthcare workers, emergency responders).

(6) Close contact of anyone known to have SARS-CoV-2 infection within 30 days prior to vaccine administration.

(7) Living in a group care facility (eg, assisted living or nursing home).

(31) A positive urine drug screen without evidence of corresponding prescribed concomitant medication(s) at Screening. Note: A positive drug screen result with a corresponding prescribed concomitant medication will be allowed if, in the opinion of the investigator and Medical Monitor, the concomitant medication does not make the subject unsuitable to participate in the clinical trial.

(32) Positive alcohol screen.

(33) Positive screen for HIV-1 and HIV-2 antibodies, HBsAg, or HCV antibody (Parts A and B). For Part C, subjects known to be HIV positive or have active Hepatitis B or C infection will be excluded.

5.3 Screen Failures

Subjects who are discontinued from the study prior to study vaccine administration will be considered screen failures and may be re-screened as long as the subject was not discontinued from the study due to noncompliance with the protocol (eg, positive urine drugs of abuse screen, etc.). If the subject is re-screened, the subject must be re-consented and have all of the screening procedures re-performed.

Screen failure data will not be recorded in the eCRF.

5.4 Decision to Administer Second Vaccination

Prior to administering the second vaccination, subjects will have the following procedures/assessments performed:

- Inclusion/exclusion criteria recheck (including absence of acute illness or new medical condition)
- Oral temperature
- Targeted physical examination
- Vital signs
- Review of clinical safety laboratory test results to date
- Urine pregnancy test, as applicable
- Nasopharyngeal swab on Day 15 to check for SARS-CoV-2 infection (result must be received by the CRU and negative prior to the second vaccine administration).
- Medical history since last visit including AE assessment for SAEs, Grade 3 AEs or AESIs that are possibly, probably, or definitely related to study vaccine without a plausible alternative explanation
- Check of Study Halting Rules (Section 5.7.2)

All assessments must be normal or be in agreement with inclusion/exclusion criteria in order for a subject to receive the second vaccination dose.

For all of the sentinel groups, the iSRC will meet to review the sentinel subjects' safety and tolerability data through Day 8. In the event that iSRC has not met for the post Day 8 review because the entire sentinel group (n = 3) has not completed Day 8 before a sentinel subject is to receive the second vaccine on Day 22, the iSRC will meet on an ad hoc basis, to ensure there are no safety concerns and that none of the Individual Discontinuation Criteria (Section 5.5) or Study Halting Rules (Section 5.7.2) have been met, prior to the sentinel subjects receiving the second vaccine.

5.5 Individual Discontinuation Criteria

The occurrence of the following findings in an individual subject may result in discontinuation from the study vaccine. Subjects will be asked to participate in the scheduled Follow-up Visits, including at a minimum Day 365, to check safety and immunogenicity.

- Subjects experiences an SAE assessed as possibly related, probably related, or related to study vaccine without a plausible alternative explanation.
- Subject has generalized urticaria during the 7-day post vaccination period.
- Subject develops a Grade 4 local reaction for which there is no alternative plausible explanation.
- Subject experiences laryngospasm, bronchospasm, or anaphylaxis after vaccine administration considered related to the vaccine.
- Subject develops a fever >40°C/104°F during the 7 days post vaccination period that is assessed as possibly related, probably related, or related to study vaccine without a plausible alternative explanation.
- Single Grade 3 AEs or AESIs that are possibly, probably, or definitely related to study vaccine without a plausible alternative explanation.
- Subject experiences any Grade 3 or higher abnormality in the same laboratory parameter determined by the Investigator or medical monitor as clinically significant and that are assessed as possibly related, probably related, or related to study vaccine without a plausible alternative explanation.

5.6 Subject Withdrawal

Subjects are free to withdraw from the study at any time, for any reason, and without prejudice to further treatment. The Investigator may withdraw a subject if, in the Investigator's judgment, continued participation would pose unacceptable risk to the subject or to the integrity of the study data. All procedures for early withdrawal must be completed. Reasons for withdrawal may include:

- AE
- SAE that is possibly related, probably related, or related, without a plausible alternative explanation
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Study terminated by Sponsor
- Withdrawal by subject
- Death
- Other

Subjects who are withdrawn for reasons other than AEs may be replaced.

In the event of a subject's withdrawal from study vaccine, the Investigator will promptly notify the Sponsor and will make every effort to complete the EOS assessments, unless the subject withdraws consent. All withdrawn subjects with ongoing clinically significant clinical or laboratory findings will be followed until the finding is resolved or medically stable; reasonable attempts will be made to follow-up with subjects. The subject will also be asked to participate in a Follow-up Visit at approximately Day 365 to check safety and immunogenicity.

Subjects may be withdrawn from receiving the second dose of the study vaccine if they meet specific Study Halting Rules (see Section 5.7.2) or Individual Discontinuation Criteria (Section 5.5). If a subject is withdrawn due to meeting a Study Halting Rule or Individual Discontinuation Criteria, they will be asked to participate in the scheduled Follow-up Visits, including at a minimum Day 365, to check safety and immunogenicity.

5.7 Independent Safety Review Committee, Study Stopping Rules, and Study Termination

5.7.1 Independent Safety Review Committee

A safety review will be performed by the iSRC according to details established at the start of the study and provided in the iSRC charter. The Investigator will provide a brief summary to the iSRC of any pertinent safety events prior to the iSRC meeting. The three member iSRC will consist of, at a minimum, two physicians with experience in vaccines and one statistician.

The iSRC will review the safety and tolerability data through Day 8 for each of the sentinel subject groups prior to the enrollment of the remaining cohort subjects. In the event that iSRC has not met for the post Day 8 review because the entire sentinel group (n = 3) has not completed Day 8 before a sentinel subject is to receive the second vaccine on Day 22, the iSRC will meet on an ad hoc basis, to ensure there are no safety concerns and that none of the Individual Discontinuation Criteria (Section 5.5) or Study Halting Rules (Section 5.7.2) have been met, prior to the sentinel subjects receiving the second vaccine.

The iSRC will be convened to review all available safety data including solicited AEs, unsolicited AEs, SAEs, MAAEs, NOCDs, AESIs, vitals, safety laboratory, and physical exams results of Part A low dose when all subjects have received the first vaccination and have all safety data through Day 8. If there are no safety concerns after the iSRC meeting, study enrollment will continue to Part A high dose and Part B low dose. The same strategy will be used to move from Part B low dose to Part B high dose.

The iSRC will also meet when a minimum of 23 subjects have completed Day 29 after the second vaccination for Part A (high and low dose) and for Part B (high and low dose) to review safety data to ensure that there are no concerns.

The iSRC will be asked to review unblinded immunogenicity and safety data when the first 30 subjects vaccinated in the Part A low dose group (including active and placebo subjects) have data available from Day 1 through Day 43 for an assessment of the risk-benefit of the trial. For the

interim analysis, treatment codes will only be unblinded by treatment group (not by individual subjects) and only after the data are deemed ready for the analysis and the data has been monitored. The unblinded review will be completed by the iSRC only and the other team members (CRO [except for the unblinded team members preparing the data for unblinded iSRC review], Investigator, and site personnel) will remain blinded. The Sponsor will be unblinded at the interim analysis (Day 43). The iSRC/Sponsor will communicate immunogenicity data to the study team in a blinded manner so that clinical development decisions for additional studies can be made by the Sponsor.

Cohort dose continuation/escalation will only occur if the iSRC determines that the current dose was safe and well tolerated. If justified by cumulative safety and tolerability data, the iSRC can dose escalate per protocol, select an intermediate dose (lower or higher), or repeat a dose. The decision to allow dose continuation/escalation into the next cohort will be documented and this decision, along with the safety information, will be communicated to the site.

The iSRC will also meet on an ad hoc basis if any of the Study Halting Rules are met (Section 5.7.2). If a Study Halting Rule is met, the iSRC will proceed with an unblinded review of available safety data. After the meeting, the iSRC will make 1 or more of the following recommendations:

- All vaccinations should resume
- Specific treatment groups should be discontinued while other treatment groups should resume vaccinations
- No vaccinations should resume
- Modifications to study conduct (eg, additional safety or laboratory assessments)

The blinded medical monitor will also assess cumulative safety information for this study per the Medical Monitoring Plan and advise the Sponsor of any of the safety findings (Section 5.7.2) have occurred.

The iSRC will review unblinded safety data for any subject who dies, requires ICU admission due to SARS-CoV-2 infection, develops an AESI (Section 8.2.2) of autoimmune disease or potential immune-medicated medical condition (Appendix B), or experiences vaccine-associated enhanced respiratory disease. If the subject had received TAP-COVID-19, the iSRC may decide whether a study halt for vaccine-enhanced disease is required based on a review of all available clinical and preclinical safety and immunogenicity data.

5.7.2 Study Halting Rules

The occurrence and confirmation of 1 or more of the following findings will result in suspension of further enrollment and study vaccine administration pending urgent review (within 1 week) of the safety data by the iSRC. Subjects who are withdrawn from study vaccine (if applicable) will continue to be monitored (Section 5.6) for safety and immunogenicity.

1. One or more subjects experience an SAE assessed as possibly related, probably related, or related to study vaccine without a plausible alternative explanation.

2. One or more subjects have generalized urticaria during the 7-day post vaccination period.
3. One or more subjects develop a Grade 4 local reaction for which there is no alternative plausible explanation.
4. One or more subjects experiences laryngospasm, bronchospasm, or anaphylaxis after vaccine administration considered related to the vaccine.
5. One or more subjects develop a fever >40°C/104°F during the 7 days post vaccination period that is assessed as possibly related, probably related, or related to study vaccine without a plausible alternative explanation.
6. Two or more subjects within an individual treatment group, or 2 or more subjects across treatment groups, experience any Grade 3 or higher abnormality in the same laboratory parameter determined by the Investigator or medical monitor as clinically significant and that are assessed as possibly related, probably related, or related to study vaccine without a plausible alternative explanation.

   Note: An unblinded statistician or designee will assist with determining whether stopping rule #6 is met.
7. Two or more subjects across treatment groups experience a Grade 3 or higher AE, MAAE, or AESI of the same or similar preferred terms (as categorized by MedDRA) assessed as possibly related, probably related, or related to study vaccine without a plausible alternative explanation.
8. Any subject with severe SARS-CoV-2 infection will be assessed for the possibility of vaccine-associated enhanced respiratory disease. Severe SARS-CoV-2 infection is defined as individuals who have virologically confirmed SARS-CoV-2 infection with any of the following:
   - Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 breaths per minute, heart rate ≥ 125 bpm, $SpO_2 \leq 93\%$ on room air at sea level or $PaO_2/FiO_2 < 300$ mmHg)
   - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or ECMO)
   - Evidence of shock (systolic blood pressure < 90 mmHg, diastolic blood pressure < 60 mmHg, or requiring vasopressors)
   - Significant acute renal, hepatic, or neurologic dysfunction
   - Admission to an ICU
   - Death due to SARS-CoV-2 infection

5.7.3 Study Termination

The study may be terminated at any time by the Sponsor if serious side effects occur, if potential risks to study participants are identified, if the Investigator does not adhere to the protocol, or if, in the Sponsor's judgment, there are no further benefits to be achieved from the study. In the event

that the clinical development of the study vaccine is discontinued, the Sponsor shall inform all Investigators/institutions and regulatory authorities.

6 TREATMENT OF SUBJECTS

6.1 Identity of Study Vaccines

The TAP-COVID-19 vaccine is comprised of a purified recombinant SARS-CoV-2 RBD-Fc conjugated to a TMV NtK carrier. The TAP-COVID-19 vaccine will be combined with CpG 7909 adjuvant prior to administration.

The product will be formulated and shipped as multi-dose vials. The vaccine doses will be diluted as appropriate by the site pharmacist to 15 μg or 45 μg doses of antigen along with 0.5 mg CpG adjuvant to be delivered in a single 0.5 mL IM injection. A detailed description for vaccine preparation is provided in the pharmacy manual.

Buffered saline solution (with thimerosal) will be used as placebo.

A description of the study vaccines is presented in Table 6-1.

Table 6-1 Study Vaccines

Study Vaccine	Dosage Form (Volume, Route)	TAP-COVID-19 Dose	Manufacturer
TAP-COVID-19 + CpG (0.5 mg)	Injectable solution, (0.5 mL, intramuscular injection)	15 μg	Kentucky BioProcessing, Inc.
TAP-COVID-19 + CpG (0.5 mg)	Injectable solution, (0.5 mL, intramuscular injection)	45 μg	Kentucky BioProcessing, Inc.
Placebo (buffered saline solution)	Injectable solution, (0.5 mL, intramuscular injection)	Not applicable	Kentucky BioProcessing, Inc.

TAP-COVID-19, CpG adjuvant, and the placebo (buffered saline solution) will be sourced by KBP.

6.2 Treatments Administered

Both Part A (18-49 years) and Part B (50-85 years) will be randomized in a 2:1 ratio (active:placebo) for each treatment dose (15 μg and 45 μg TAP-COVID-19 vaccine + 0.5 mg CpG) for a total of 90 subjects per Part (30 subjects 15 μg TAP-COVID-19 vaccine + 0.5 mg CpG:30 subjects 45 μg TAP-COVID-19 vaccine + 0.5 mg CpG:30 subjects placebo).

Treatment A: TAP-COVID-19 vaccine (15 μg) + CpG (0.5 mg) IM injection on Day 1 and Day 22 (±3 days)

Treatment B: TAP-COVID-19 vaccine (45 μg) + CpG (0.5 mg) IM injection on Day 1 and Day 22 (±3 days)

Treatment C: Placebo (buffered saline solution) IM injection on Day 1 and Day 22 (±3 days)

The IM dose for Part C Expansion (optional) will be determined after reviewing the safety and immunogenicity data through Day 43 from Parts A and B (low and high dose).

6.3 Method of Assigning Subjects to Treatment Groups

ICON will prepare the randomization scheme in accordance with its SOPs and the randomization plan, which reflect GCP standards. Refer to Section 9.3 for a description of randomization methods. Eligible subjects will be assigned to a treatment group according to the list of subject randomization assignments.

6.4 Measurements of Treatment Compliance

All study vaccine doses will be prepared and administered by delegated and trained staff at the clinical site(s). Details regarding dosing, including the dose administered and the date and time of dosing, will be recorded.

6.5 Study Vaccine Storage, Accountability, and Retention

6.5.1 Storage Conditions

The Investigator will ensure that all the study vaccines are stored per the instructions accompanying the study vaccine. In addition, the Investigator will ensure that study vaccines are handled in accordance with the FDA regulations concerning the storage and administration of investigational products.

Refer to the SRM for additional study vaccine storage instructions.

6.5.2 Drug Accountability and Retention

The Investigator must ensure that all study vaccine supplies are kept in a secure locked area with access limited to those authorized by the Investigator. The Investigator must maintain accurate records of the receipt of all study vaccine shipped by KBP or their representative, including but not limited to the date received, lot number, expiration date, amount received, and the disposition of all study vaccine. Current dispensing records will also be maintained including the date and amount of study vaccine dispensed and the subject receiving the drug. All remaining study vaccine not required by regulations to be held by the clinical site(s) must be returned to KBP or their representative immediately after the study is completed.

6.6 Packaging and Labeling

6.6.1 Study Vaccine

Study vaccine will be supplied as a concentrated injectable solution packaged in 10-mL multi-dose vials with preservative (thimerosal). CpG sterile solution will be supplied as a concentrated solution with preservative (thimerosal). Placebo will be buffered saline solution with preservative (thimerosal) provided by KBP.

6.6.2 Blinding of Treatment Assignment

ICON will maintain the randomization code in a secure location with controls to prevent unauthorized access, including the computer program written to generate the randomization, randomization codes, program log, seed number used by the program, copy of the randomization plan along with approval documentation as appropriate, and the write-protected electronic storage medium.

The site and CRO will name an unblinded statistician to provide the randomization code. The pharmacists will be unblinded. Since the placebo and vaccine will not be identical in appearance, the staff member administering the doses will be unblinded and will not participate in any additional study activities. In order to preserve the blind, study vaccine will be prepared and administered in a manner that masks the content for both the subject and any observers. Investigators, site staff, subjects, CRO [except for the unblinded team members preparing the data for unblinded iSRC review] will remain blinded until the completion of the study. The Sponsor will remain blinded to individual subjects' treatment assignment from the beginning of the study through Day 43. When the data is unblinded for the interim analysis after all subjects complete Day 43, the Sponsor will be unblinded.

6.6.3 Unblinding of Treatment Assignment

6.6.3.1 Unblinding for Adverse Event/Safety Reasons

Should an SAE or other circumstance require that the blind be broken to ensure subject safety, the Investigator must immediately notify the medical monitor and/or Sponsor. ICON/designee will notify the Sponsor as soon as possible and will release the treatment assignment of the subject to the appropriate personnel in accordance with the applicable SSP.

If the treatment assignment is unblinded by the site pharmacist or any party other than ICON, the Investigator must notify ICON in writing and document the course of events in the source records. Any subject for whom the treatment code is prematurely released will be withdrawn from the study.

6.6.3.2 Unblinding for Interim Analyses

An unblinded interim analysis will be performed on the safety and immunogenicity data collected for each of the 4 dose groups (Part A low dose, Part A high dose, Part B low dose, and Part B high dose). Unblinded interim analysis will occur for the Part A low dose group (including active and placebo subjects) when the first 30 subjects vaccinated have data available from Day 1 through Day 43. The remaining cohorts will have an unblinded interim analysis performed when all subjects in the cohort have data from Day 1 through Day 43. For the interim analysis, treatment codes will be unblinded after the data are deemed ready for the analysis and the data has been monitored The CRO [except for the unblinded team members preparing the data for unblinded iSRC review], Investigator, and clinical staff will not have access to the unblinded treatment group interim analyses and will remain blinded until completion of the study. The Sponsor will be unblinded at the interim analysis. The iSRC will communicate immunogenicity data to the study

team in a blinded manner so that clinical development decisions for additional studies can be made by the Sponsor.

6.7 Concomitant Medications and Procedures and Other Restrictions

6.7.1 Concomitant Medications and Procedures

Any medication taken by a subject from 30 days prior to the screening visit through the first 43 days of the study and the reason for its use will be documented.

Previous prescription medication for mild chronic health disorders (eg, hypertension or hypercholesterolemia) or maintenance (eg, contraception) will be allowed at the discretion of the Investigator as long as the subject has been on a stable dose for at least 3 months. Subjects should continue their regular maintenance medications throughout study participation unless instructed to discontinue or change by the Investigator or their personal physician. If concomitant medications are discontinued by a subject during study conduct the subject should notify the Investigator. Subjects should refrain from starting new medications, modifying current concomitant medications, or receiving vaccinations during study participation unless prescribed by the Investigator for treatment of specific clinical events.

Subjects should not receive any vaccine within 1 month before screening.

Subjects should not be using prescription medications for the prophylaxis of SARS-CoV-2.

Subjects should not participate or plan to participate in a study that involves an experimental agent (vaccine, drug, biologic, device, or medication); or should not have received an experimental agent within 1 month before enrollment in this study; or who expect to receive another experimental agent during participation in this study.

A positive drug screen result with a corresponding prescribed concomitant medication will be allowed if, in the opinion of the investigator and Medical Monitor, the concomitant medication does not make the subject unsuitable to participate in the clinical trial.

6.7.2 Other Restrictions

Subjects will be instructed to adhere to the following restrictions:

- Strenuous activity (as assessed by the Investigator) is prohibited from 48 hours prior to the days safety laboratory blood will be collected
- Subjects are not permitted to consume alcohol for 3 days prior to vaccination and should refrain from consumption of alcohol until 7 days post vaccination.
- Subjects should refrain from blood donation for 6 months post vaccination.
- Subjects should not participate or plan to participate in a study that involves an experimental agent (vaccine, drug, biologic, device, or medication); or should not have received an experimental agent within 1 month before enrollment in this study; or who expect to receive another experimental agent during participation in this study.

7 STUDY ASSESSMENTS AND PROCEDURES

Subjects will undergo study procedures and assessments at time points specified in the Schedule of Assessments and Procedures (Table 1-1).

7.1 Pandemic Safety Procedures

Appropriate measures will be taken to ensure the safety of both study staff and study subjects including social distancing and appropriate personal protective equipment.

7.2 Medical and Surgical History

The Investigator or designee will collect a complete medical and surgical history at screening. Medical and surgical history will be collected at CRU visits to determine if any changes have occurred since screening.

7.3 Demographic Characteristics

Demographic characteristics including sex, age, race, and ethnicity will be recorded. Tobacco use and history will also be documented.

7.4 Physical Measurements

Height (cm) and body weight (kg) without shoes will be recorded. BMI will be calculated using the height obtained at screening.

7.5 Immunogenicity

Blood samples for antibody titers will be collected per Table 1-1 to assess:

- Vaccine (ELISA for IgM and IgG, total antibody) and neutralizing antibody titers (virus microneutralization) for each treatment group:
  - GMT ratio ($GMT_{placebo}/GMT_{TAP\text{-}COVID\text{-}19}$)
  - Seroconversion rate is defined as the proportion of subjects at the respective time point that have detectable antibodies (IgG and IgM) against SARS-CoV-2 Spike Protein RBD following challenge with vaccine (and potentially by natural asymptomatic or symptomatic infection by the virus in case of a placebo subject).
- Anti-RBD and anti-Fc antibodies

Blood samples for cellular immunity (PBMCs) will be collected per Table 1-1. The numbers of cytokine producing CD4+ and CD8+ T-cells from PBMCs responsive to vaccine antigens will be analyzed using a validated procedure.

PBMC and serum samples for future research will also be collected (5-7 aliquots [1 mL]) at the time points outlined in Table 1-1.

Immunogenicity sample collection, processing, and shipping details will be outlined in a separate SRM.

7.6 SARS-CoV-2 Exposure and Asymptomatic Monitoring

Subjects will be monitored for SARS-CoV-2 exposure for potential asymptomatic infection throughout the study. CRU staff will interview subjects about any potential exposure to the virus. If a subject has had potential exposure, the CRU will perform an unscheduled nasopharyngeal swab. Subjects will not be discontinued from the study due to positive SARS-CoV-2 test results.

- If a subject has a positive or borderline ELISA anti-N IgG result, sites should have the subject return for an unscheduled PCR. If the ELISA is positive and the PCR is negative, the sites should follow the subjects using the standard of care under Investigator discretion, retesting ELISA at the next study visit(s) or sooner (per the Investigator's decision).

- If the subject has a positive or borderline ELISA anti-N IgG AND a positive PCR test, the clinical sites should bring the subjects back for repeat PCR testing as described below.

- The clinical sites should continue to collect PCR tests if a subject is experiencing possible COVID-19 symptoms, or had possible exposure to SARS-CoV-2 (ie, close contact tests positive for SARS-CoV-2). Testing will occur every 2 weeks for a total of 4 weeks (if 2 consecutive negative tests) or until negative (x2) after a positive result. Positive results will be reported as an AESI (Section 8.2.2) and subjects followed for disease severity, duration, and outcome.

Telephone visits will be conducted to augment the in person visits through 6 months post-vaccination (Table 1-1). CRU staff will interview the subjects about any potential exposure to the virus. If a subject has had potential exposure, the CRU will ask the subject to come in for an unscheduled visit that will include a nasopharyngeal swab.

Subjects will be reminded at onsite visits and during telephone visits to contact the clinical site any time there is potential exposure to SARS-CoV-2 or they are experiencing any respiratory disease/symptoms suggestive of SARS-CoV-2 infection.

7.7 Safety Assessments

7.7.1 Adverse Events

Subjects will be monitored for AEs according to Section 8.

If a subject experiences respiratory symptoms suggestive of SARS-CoV-2 infection, the subject should notify the clinical site for a visit to collect nasopharyngeal swabs for RT-PCR virus detection.

Subjects with positive ELISA anti-N IgG results without COVID-19 symptoms may indicate asymptomatic SARS-CoV-2 infection and will be followed with the appropriate standard of care. Subjects with a positive ELISA anti-N IgG result should have a PCR test and be followed until both are negative as in the protocol instructions (Section 7.6).

7.7.2 Reactogenicity Assessments

Subjects will keep a Diary Card to track reactogenicity assessments for 7 days after each vaccination. Reactogenicity assessments include generalized symptoms such as headache, fatigue, muscle pain, joint pain, nausea, chills, fever, and rash (not at injection site), and localized reactions including pain, erythema, induration, and swelling. If an AE continues after 7 days, the AE will be captured as ongoing/continuing (not noted as a new AE).

7.7.3 Laboratory Tests

A certified laboratory will be utilized to process and provide results for the clinical safety laboratory tests listed in Table 7-1. The baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the first dose of study vaccine.

Subjects will fast a minimum of 8 hours prior to clinical laboratory sample collection at screening.

During the screening period, if a subject has an out-of-range value for a clinical safety laboratory parameter that the Investigator believes is not clinically significant or the Investigator does not believe is correct (eg, lab or specimen processing error), but the Investigator wants to confirm with a repeat laboratory test, a single repeat is allowed to confirm the initial result.

If Part C Expansion (optional) is performed, all Part C subjects will have safety laboratory tests performed at screening only in order to satisfy the inclusion/exclusion criteria. In addition, the first 200 subject in Part C will have safety laboratory tests performed at all time points. The remaining subjects in Part C will not have safety laboratory tests performed at any of the post-dose time points unless the Investigator deems it necessary.

Additional safety laboratory tests may be conducted as needed by the Investigator to evaluate subject safety.

Table 7-1 Clinical Safety Laboratory and Screening Tests

Hematology	Chemistry		Urinalysis
Hematocrit Hemoglobin Red blood cell count White blood cell count Neutrophils (absolute) Lymphocytes (absolute) Monocytes (absolute) Basophils (absolute) Eosinophils (absolute) Platelet count (estimate not acceptable)	Albumin Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Gamma glutamyl transferase Direct bilirubin Total bilirubin Lactate dehydrogenase Total protein	Blood urea nitrogen Creatinine Calcium Phosphate Sodium Potassium Carbon dioxide Chloride Glucose [a] Total cholesterol Triglycerides [a]	Specific gravity Ketones pH Protein Blood Glucose Leukocyte esterase Microscopic analysis (performed if blood, leukocytes, or protein are present)
Urine Drugs of Abuse[b,c]	**Serology [d]**	**Other**	
Barbiturates Cocaine Tetrahydrocannabinol Amphetamines Opiates Phencyclidine	HIV-1 HIV-2 HBsAg HCV antibody	Prothrombin Pregnancy test Follicle-stimulating hormone [e] Alcohol screen[c]	

a. Fasting required at screening only
b. At a minimum, these tests must be included
c. During the screening period, urine drugs of abuse and alcohol screens may not be repeated for eligibility
d. Includes any confirmatory tests performed at the discretion of the Investigator
e. As needed to confirm postmenopausal status

For any laboratory test value outside the reference range that the Investigator considers clinically significant during the on-study period (ie, following dose administration), the Investigator will:

- Repeat the test to verify the out-of-range value and clinical significance.
- Follow the out-of-range value until the value returns to normal or baseline, or until the value is deemed stable and not clinically significant by the Investigator.
- Record as an AE any laboratory test value that is confirmed by repeat and the Investigator considers clinically significant, requires a subject to be discontinued from the study, requires a subject to receive treatment, or requires a change or discontinuation of the study vaccine (if applicable).

7.7.4 Vital Signs

Vital signs assessments will include systolic and diastolic blood pressure (mmHg), heart rate (bpm), respiratory rate (breaths per minute), and oral temperature (C°). In addition, oral temperature will be performed prior to each vaccination. Vital signs will be measured after the subject has been resting quietly in a seated position for at least 5 minutes. Any clinically significant abnormal vital sign assessment requires at least one repeat measurement.

A vital signs abnormality that is considered clinically significant initially and on confirmation, requires a subject to be discontinued from the study, requires a subject to receive treatment, or requires discontinuation from the study vaccine (if applicable) will be recorded as an AE.

7.7.5 Physical Examination

Comprehensive physical examinations (excluding genital, rectal, and breast examinations [unless indicated]) will be performed, and abnormal findings will be documented in the subject's eCRF.

Targeted physical examinations will focus on any AEs ongoing at the time of the examination (Table 1-1).

An abnormal physical examination finding that is considered clinically significant and requires the subject to be discontinued from the study, requires the subject to receive treatment, or requires discontinuation of the study vaccine (if applicable) will be recorded as an AE.

7.7.6 Appropriateness of Safety Assessments

Safety evaluations selected for this study are typical of those for this subject population and utilize widely accepted measures.

8 ADVERSE EVENTS

An AE is defined as any untoward medical occurrence in a subject administered a pharmaceutical product during the course of a clinical investigation. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a study vaccine, whether or not thought to be related to the study vaccine. A TEAE is any AE that occurs after the first dose of study drug, regardless of relationship to the study drug.

MAAEs are AEs for which the subject has received medical attention by medical personnel, or in an emergency room, or which led to hospitalization. For each reported AE, the Investigator will ask the subject if such medical attention has been received. In addition, the Investigator will assess each MAAE if it constitutes a NOCD, defined as a MAAE that was:

- absent at baseline,
- not resolved at EOS
- required continuous medical care or attention.

Subjects will be monitored throughout the study for AEs, from the first dose of study vaccine through Day 43 of the study and for SAEs, MAAEs, NOCDs, and AESIs from the first dose through the end of the study (Day 365 ±14 days). Adverse events that are identified at the last assessment visit (or the early termination visit) as specified in the protocol must be recorded on the AE eCRF with the status of the AE noted. All events that are ongoing at this time will be recorded as ongoing on the eCRF. All (both serious and nonserious) AEs must be followed until they are resolved or medically stable, or until reasonable attempts to determine resolution of the event are exhausted. The Investigator should use his/her discretion in ordering additional tests as necessary to monitor the resolution of such events.

The procedures specified in Section 8.4 are to be followed for reporting SAEs.

8.1 Recording Adverse Events

Adverse events are to be recorded on the AE page of the eCRF. The following information will be recorded:

- Assessment of whether or not the AE is an SAE, MAAE, NOCD, or AESI (Section 8.2.1)
- Assessment of AE intensity (Section 8.2.2)
- Assessment of AE relationship to study vaccine (Section 8.2.4)
- Action taken - dose not changed, vaccine dose 2 not given, not applicable, or unknown, as applicable
- Outcome - recorded as fatal, not recovered/not resolved, recovered/resolved, recovered/resolved with sequelae, recovering/resolving, or unknown, as applicable

8.2 Assessment of Adverse Events

The Investigator will assess each AE for seriousness, intensity, and relationship to study vaccine.

8.2.1 Serious Adverse Events, Medically Attended Adverse Events, New Onset Chronic Medical Conditions, Adverse Events of Special Interest, and Potential Immune-mediated Conditions

The Investigator is responsible for determining whether an AE meets the definition of an SAE, MAAE, NOCDs, or AESIs including potential immune-mediated medical condition from the first dose of the study vaccine through the end of the study (Day 365 ±14 days).

An SAE is any AE that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

MAAEs are defined as hospitalization, an emergency room visit, or an otherwise unscheduled visit to or from medical personnel for any reason.

NOCDs are defined as any new ICD diagnosis (per current International Statistical Classification of Diseases and Related Health Problems) that is applied to the subject during the course of the study, after receipt of the study agent, that is expected to continue for at least 3 months and requires continued health care intervention.

AESIs are defined in Section 8.2.2 and a list of potential immune-mediated medical conditions is provided in Appendix B.

Note: SAEs, MAAEs, NOCDs, and AESIs including potential immune-mediated medical conditions require immediate reporting to the medical monitor and/or Sponsor. Refer to Section 8.4 for details.

8.2.2 Adverse Events of Special Interest

An AESI is any AE that a regulatory authority has mandated be reported on an expedited basis (including to the iSRC), regardless of the seriousness, expectedness, or relatedness of the AE to

the administration of investigational product. To date, no AESIs have been identified specifically for the TAP-COVID-19 vaccine + CpG adjuvant. However, subjects who test positive for COVID-19, present with autoimmune disease, or are diagnosed with a potential immune-mediated medical condition (Appendix B) should be reported as AESI.

AESIs will be followed as per the procedures in the study protocol, SRM, and/or SAE SSP for SAEs and pregnancy reporting, regardless of the seriousness, expectedness, or relatedness of the AESI to the administration of study vaccine. AESIs will be reported by the site directly to the Sponsor, medical monitor, and SAE hotline at ICON (ICON Pharmacovigilance) (Section 8.4).

Subjects positive for SARS-CoV-2 will not be discontinued. Positive SARS-CoV-2 cases will be followed and include referral to a primary care physician, collection of all medical records, assessment of severity, and review by the site investigator and medical monitor. All positive SARS-CoV-2 cases will also be shared with the iSRC on an ongoing basis.

8.2.3 Intensity

The intensity of an AE will be graded according to Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007). The grading scale is comprised of 4 levels: mild (Grade 1), moderate (Grade 2), severe (Grade 3), and potentially life-threatening (Grade 4). For those AEs that are not covered in the Guidance for Industry (above) the rating scale from DAIDS (Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1) will be used (Table 8-1).

Table 8-1 DAIDS Adverse Events Intensity Assessment

Grade	Intensity	Definition
Grade 1	Mild	Symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated.
Grade 2	Moderate	Symptoms causing greater than minimal interference with usual social and functional activities with intervention indicated.
Grade 3	Severe	Symptoms causing inability to perform usual social and functional activities with intervention or hospitalization indicated.
Grade 4	Potentially Life-Threatening	Symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death.
Grade 5		Any AE where the outcome is death

8.2.4 Relationship to Study Vaccine

The relationship of an AE to the study vaccine should be determined by the Investigator according to the following criteria:

- Not related: The event is most likely produced by other factors such as the subject's clinical condition, intercurrent illness, or concomitant drugs, and does not follow a known response pattern to the study vaccine, or the temporal relationship of the event to study vaccine administration makes a causal relationship unlikely

- Related: The event follows a reasonable temporal sequence from the time of drug administration, and/or follows a known response pattern to the study vaccine, and cannot be reasonably explained by other factors such as the subject's clinical condition, intercurrent illness, or concomitant drugs

8.3 Discontinuation Due to Adverse Events

Any subject who experiences an AE may be withdrawn at any time from the study at the discretion of the Investigator. Subjects withdrawn from the study due to an AE, whether serious or nonserious, may be followed by the Investigator until the clinical outcome of the AE is determined. The subject will also be asked to participate in a Follow-up Visit at approximately Day 365 to check safety and immunogenicity. The AE(s) should be noted on the appropriate eCRFs, the subject's progress should be followed until the AE is resolved or medically stable as determined by the Investigator, and the Sponsor notified.

8.4 Reporting Serious Adverse Events and Adverse Events of Special Interest

In the event of any SAE or AESI reported or observed during the study, whether or not attributable to the study vaccine, site personnel will report it immediately by telephone to the Sponsor, medical monitor, AND SAE hotline at ICON (ICON Pharmacovigilance) in accordance with procedures described in the SRM and/or SAE SSP. Site personnel will follow up with a written report on the next working day.

Report Forms will be provided to the CRU to assist in collecting, organizing, and reporting SAEs or AESIs and follow-up information.

All SAEs and AESIs should be followed to their resolution, with documentation provided to the Sponsor/ICON on a follow-up Report Form.

8.5 Pregnancy

Pregnancies will be captured if they occur in female subjects from the time the subject is first exposed to the study vaccine until EOS. Pregnancies in the sexual partners of male subjects will be captured from the time the subject is first exposed to the study vaccine until 90 days after last exposure to the study vaccine.

Female subjects must be instructed to inform the study Investigator immediately if they become pregnant during the study.

The Investigator must report any pregnancy to the medical monitor, Sponsor, and ICON Pharmacovigilance within 1 business day of becoming aware of the pregnancy per pregnancy reporting procedures described in the SRM. The subject must be immediately discontinued from further treatment with study vaccine. An uncomplicated pregnancy will not be considered an AE or SAE; however, all pregnancies will be followed through birth and 3 months postdelivery.

Any congenital abnormalities in the offspring of a subject who received study vaccine will be reported as an SAE. The outcome of any pregnancy and the presence or absence of any congenital

abnormality will be recorded in the source documentation and reported to the Sponsor and ICON Pharmacovigilance.

8.6 Drug-induced Liver Injury

Subjects will be monitored for signs of DILI. Study vaccine (dose 2) will be withheld in the event of potential DILI.

Potential events of DILI will be defined as meeting all of the following criteria (as specified in the FDA Guidance for Industry Drug-induced Liver Injury: Premarketing Clinical Evaluation, 2009):

- ALT or AST >3 × ULN
- Total bilirubin >2 × ULN without initial findings of cholestasis (elevated serum ALP)
- No other reason can be found to explain the combination of laboratory value increases (eg, acute viral hepatitis; alcoholic and autoimmune hepatitis; hepatobiliary disorders; nonalcoholic steatohepatitis; cardiovascular causes; concomitant treatments)

Potential events of DILI will be reported as SAEs (Section 8.4). All subjects with potential DILI will be closely followed until abnormalities return to normal or baseline or until reasonable attempts to determine resolution of the event are exhausted.

9 STATISTICAL CONSIDERATIONS

The statistical analysis will be conducted following the principles as specified in ICH Topic E9 (CPMP/ICH/363/96).

All statistical analyses will be described in a separate SAP.

The statistical evaluation will be performed using SAS® software version 9.4 or higher (SAS Institute, Cary, NC). All data will be listed, and summary tables will be provided. No formal significance testing will be performed. Summary statistics will be presented by treatment group and include subset analysis (eg, all subjects, seronegative subjects [ie, neutralizing antibody titer < 10 at screening], seropositive subjects, and subjects that received an FDA Emergency Use Authorization/licensed COVID vaccine). For continuous variables, data will be summarized with the number of subjects, mean, standard deviation, median, minimum, maximum, geometric mean, CV%, GeoCV%, and 95% CI by treatment group. For categorical variables, data will be tabulated with the number and proportion of subjects for each category by treatment group.

The database will be locked and unblinded after the data have been monitored for all subjects through Day 43. Details of the unblinded interim analysis are presented in Section 9.5.

The final analysis of the safety and immunogenicity data collected from Day 43 through Day 365/approximately 1 year after first vaccination will be performed after the study is completed. An addendum to the initial CSR will be prepared with data from final analysis. Details of the statistical analyses, methods, and data conventions will be described in the SAP.

9.1 Sample Size Calculation

No formal sample size calculation was performed.

A total of 180 subjects will be enrolled in Parts A and B. Approximately 90 eligible subjects (aged 18-49 years), with 30 subjects per treatment group for Part A and 90 eligible subjects (aged 50-85 years), with 30 subjects per treatment group for Part B, will be enrolled in the study.

An optional Part C Expansion may be conducted to confirm the safety and immunogenicity of the selected dose of vaccine in up to 1000 adult subjects randomized 1:1 (single dose level of study vaccine:placebo). The proposed sample size was selected based on WHO guidelines on clinical evaluation of vaccines: regulatory expectations Annex I (2001), which states that approximately 300 subjects are needed to identify common local reactogenicity events. A larger sample size will assist in a better characterization of kinetics and range of immunity (neutralizing antibody titers) and provide a more reliable output of seropositivity and seroconversion to TAP-COVID-19 immunization. With the limited clinical experience with SARS-CoV-2 vaccines and the current lack of a biomarker correlate of protection, the generation of this larger data set is relevant to inform the design and implementation of a Phase 3 program.

9.2 Analysis Populations

Enrolled Population: All subjects who signed the ICF.

Safety Population: All subjects who provide consent, are randomized, and receive any amount of study vaccine/placebo. The Safety Population will be used for the demographic, baseline characteristic, safety data summaries, and the analysis of primary endpoints such as occurrence of solicited local and systemic reactogenicity.

Per Protocol (PP) Population: Includes all subjects in the Safety Population who receive the assigned doses of the study vaccine/placebo according to protocol, have serology results, and have no major protocol deviations affecting the primary immunogenicity outcomes, as determined by the Sponsor before database lock and unblinding. Subjects that are immunized with an approved vaccine will be captured as a subset analysis of the PP Population at Days 90, 181, 273, and 365 based on the date of receiving an approved COVID-19 vaccine.

Modified Intent-to-Treat (mITT) Population: Includes all subjects in the Safety Population who provide any serology data. The mITT Population will be used for the immunogenicity analysis.

9.3 Randomization

The overall randomization for the study will be 2:1 (active:placebo). Each Part (A and B) and treatment (low and high) will be randomized individually 2:1 (active to placebo).

The study will start with Part A (18-49 years) low dose, randomized in a 2:1 ratio (30 subjects active:15 subjects placebo) for Treatment A (15 µg TAP-COVID-19 vaccine + 0.5 mg CpG).

Part A (18-49 years) high dose will be randomized in a 2:1 ratio (30 subjects active:15 subjects placebo) for Treatment B (45 µg TAP-COVID-19 vaccine + 0.5 mg CpG) after Part A low dose has completed enrollment and the iSRC has reviewed safety and tolerability data through Day 8.

Part B (50-85 years) low dose will be randomized in a 2:1 ratio (30 subjects active:15 subjects placebo) for Treatment A (15 µg TAP-COVID-19 vaccine + 0.5 mg CpG) after Part A low dose has completed enrollment and received the first vaccination and the iSRC has reviewed safety data through Day 8.

Part B (50-85 years) high dose will be randomized in a 2:1 ratio (30 subjects active:15 subjects placebo) for Treatment B (45 µg TAP-COVID-19 vaccine + 0.5 mg CpG) after Part B low dose has completed enrollment and received the first vaccination and the iSRC has reviewed safety data through Day 8.

A total of 90 subjects will be randomized in Part A (18-49 years); 30 subjects low dose (Treatment A, 15 µg TAP-COVID-19 vaccine + 0.5 mg CpG), 30 subjects high dose (Treatment B, 45 µg TAP-COVID-19 vaccine + 0.5 mg CpG), and 30 subjects placebo (Treatment C).

A total of 90 subjects will be randomized in Part B (50-85 years); 30 subjects low dose (Treatment A, 15 µg TAP-COVID-19 vaccine + 0.5 mg CpG), 30 subjects high dose (Treatment B, 45 µg TAP-COVID-19 vaccine + 0.5 mg CpG), and 30 subjects placebo (Treatment C).

Treatment A: TAP-COVID-19 vaccine (15 µg) + CpG (0.5 mg) IM injection on Day 1 and Day 22 (±3 days)

Treatment B: TAP-COVID-19 vaccine (45 µg) + CpG (0.5 mg) IM injection on Day 1 and Day 22 (±3 days)

Treatment C: Placebo (buffered saline solution) IM injection on Day 1 and Day 22 (±3 days)

A computer-generated randomization schedule for each part (Part A, Part B, and Part C Expansion) will be generated prior to study start by an ICON biostatistician.

For sentinel dosing, 3 subjects from each part will be randomized 2:1 (active:placebo). The remainder of each cohort will also be randomized 2:1 (active:placebo).

9.4 Endpoints

Endpoints are presented in Section 3.2.

9.5 Interim Analyses

An unblinded interim analysis will be performed on the safety and immunogenicity data collected for each of the 4 dose groups (Part A low dose, Part A high dose, Part B low dose, and Part B high dose). Unblinded interim analysis will occur for the Part A low dose group (including active and placebo subjects) when the first 30 subjects vaccinated have data available from Day 1 through Day 43. The remaining cohorts will have an unblinded interim analysis performed when all subjects in the cohort have data from Day 1 through Day 43. For the interim analysis, treatment codes will be unblinded after the data are deemed ready for the analysis and the data has been monitored. The CRO [except for the unblinded team members preparing the data for unblinded iSRC review], Investigator, and clinical staff will not have access to the unblinded treatment group interim analyses and will remain blinded until completion of the study. The Sponsor will be unblinded at the interim analysis. Safety and immunogenicity analyses from this unblinded interim analysis will be presented in a CSR. This CSR may be submitted to regulatory authorities as needed.

9.6 Immunogenicity Analysis

The mITT Population will be used for all listings and summary statistics corresponding to immunogenicity analysis.

The individual sampling and blood collection for ELISA analysis to determine IgG and IgM antibody titers to the spike RBD and neutralizing antibody titers for parent (Wuhan) and any variant SARS-CoV-2 strains, will be listed and summarized by time points for each part by treatment.

All derived immunogenicity secondary endpoint parameters: GMT, GMT ratio, GMFR, GMI, and seroconversion rates will be listed and summarized by scheduled time point using descriptive statistics (n, mean, SD, minimum, median, maximum, geometric mean, CV%, GeoCV%, and 95% CI) for each part by treatment.

PBMC and serum sample data for future research results at each scheduled visit will also be provided separately in a listing and summary table, if applicable.

Subgroup analysis for safety and efficacy will be performed for those subjects who were seropositive when enrolled.

Graphical display of the summary results or at individual time points will be provided as needed (eg, scatter plots of subject titer values to visually display individual data points).

Additional details for analysis of immunogenicity are presented in the SAP.

9.7 Cellular Analysis

The number of IFN-γ and IL-5 producing T-cells (CD4+ and CD8+) from PBMCs responsive to vaccine antigens will be listed and summarized by time point using appropriate descriptive statistics for each part by treatment.

Additional details for cellular analysis are presented in the SAP.

9.8 Safety Analysis

Safety Population will be used for all safety variables specified.

All safety data will be summarized by part and treatment. No statistical tests will be performed.

Subjects who are seropositive and seronegative at screening will also be summarized and safety and efficacy subgroup analysis will be performed for these groups of subjects.

Additional details for safety analysis are presented in the SAP.

10 ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator will provide direct access to source data and documents for individuals conducting study-related monitoring, audits, IRB review, and regulatory review. The Investigator must inform the study subject that his/her study-related records may be reviewed by the above individuals without violating the subject's privacy of personal health information in compliance with HIPAA regulations.

Attention is drawn to the regulations promulgated by the FDA under the Freedom of Information Act providing, in part, that information furnished to clinical Investigators and IRBs will be kept confidential by the FDA only if maintained in confidence by the clinical Investigator and IRB. By signing this protocol, the Investigator affirms to the Sponsor that the Investigator will maintain, in confidence, information furnished to him or her by the Sponsor and will divulge such information to the IRB under an appropriate understanding of confidentiality with such board.

11 QUALITY CONTROL AND QUALITY ASSURANCE

Sponsor/ICON will implement and maintain quality control and quality assurance procedures with written SOPs to ensure the study is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, and applicable regulatory requirements.

11.1 Conduct of Study

This study will be conducted in accordance with the provisions of the Declaration of Helsinki and all revisions thereof (Tokyo 2004), and in accordance with FDA CFR (§312.50 and §312.56) and the ICH E6 Guidelines on GCP (CPMP/ICH/135/95). Specifically, this study is based on adequately performed laboratory and animal experimentation; the study will be conducted under a protocol reviewed by an IRB; the study will be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the subjects will be respected; the physicians conducting the study do not find the hazards to outweigh the potential benefits; and each subject will give his or her written, informed consent before any protocol-driven tests or evaluations are performed.

The Investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate IRB, except when necessary to eliminate immediate hazards to the subject or when the change(s) involve only logistical or administrative aspects of the study and are approved by the Sponsor. Any deviation may result in the subject having to be withdrawn from the study, and may render that subject nonevaluable.

11.1.1 Protocol Deviations

A protocol deviation is defined as any intentional or unintentional change to, or noncompliance with, the approved protocol procedures or requirements. Deviations may result from the action or inaction of the subject, Investigator, or site staff.

At the outset of the study, a process for defining and handling protocol deviations will be established. This will include determining which violations will be designated “key,” requiring immediate notification to the medical monitor and/or Sponsor. The Investigator is responsible for seeing that any known protocol deviations are recorded and handled as agreed.

11.2 Protocol Amendments

Only the Sponsor may modify the protocol. Amendments to the protocol will be made only after consultation and agreement between the Sponsor and the Investigator. All amendments that have an impact on subject risk or the study objectives, or require revision of the ICF, must receive approval from the IRB prior to their implementation.

11.3 Monitoring of Study

The Investigator will permit the CRA to review study data as frequently as is deemed necessary to ensure data are being recorded in an adequate manner and protocol adherence is satisfactory.

The Investigator will provide access to medical records for the monitor to verify eCRF entries. The Investigator is expected to cooperate with the Sponsor or a designee in ensuring the study adheres to GCP requirements.

The Investigator may not recruit subjects into the study until the Sponsor or a designee has conducted a site initiation visit (in-person or via teleconference) to review the protocol and eCRF in detail.

12 ETHICS

12.1 Institutional Review Board Approval

12.1.1 Ethics Review Prior to Study

The Investigator will ensure that the protocol and ICF are reviewed and approved by the appropriate IRB prior to the start of any study procedures. The IRB will be appropriately constituted and will perform its functions in accordance with FDA regulations, ICH GCP guidelines, and local requirements as applicable.

12.1.2 Ethics Review of Other Documents

The IRB will approve all protocol amendments (except for Sponsor-approved logistical or administrative changes), written informed consent documents and document updates, subject recruitment procedures, written information to be provided to the subjects, available safety information, information about payment and compensation available to subjects, the Investigator's curriculum vitae and/or other evidence of qualifications, and any other documents requested by the IRB and regulatory authority as applicable.

12.2 Written Informed Consent

The nature and purpose of the study will be fully explained to each subject. The subjects must be given ample time and opportunity to inquire about details of the study, to have questions answered to their satisfaction, and to decide whether to participate. Written informed consent must be obtained from each subject prior to any study procedures being performed.

13 DATA HANDLING AND RECORD KEEPING

13.1 Data Reporting and Case Report Forms

13.1.1 Case Report Forms

The Investigator will be provided with eCRFs, and will ensure all data from subject visits are promptly entered into the eCRFs in accordance with the specific instructions given. The Investigator must sign the eCRFs to verify the integrity of the data recorded.

13.1.2 Laboratory Data

A list of the normal ranges for all laboratory tests to be undertaken forms part of the documentation to be collated prior to study start. If a central laboratory has been selected to conduct any or all tests, it is essential all samples be analyzed at that laboratory. The Investigator must maintain source documents such as laboratory reports and complete history and physical examination reports.

13.1.3 Retention of Source Documents

The Investigator must maintain source documents such as laboratory reports, x-rays, ECGs, consultation reports, and complete history and physical examination reports.

13.2 Retention of Essential Documents

The study essential documents must be maintained as specified in the ICH guidelines for GCP and the applicable regulatory requirements. The Investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study vaccine. These documents should be retained for a longer period; however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

14 ADMINISTRATIVE INFORMATION

14.1 Financing and Insurance

Financing and insurance will be addressed in a separate agreement between the Sponsor and the Investigator.

14.2 Publication Policy

The Sponsor will retain ownership of all data. All proposed publications based on this study will be subject to Sponsor's approval requirements.

15 REFERENCES

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16 SIGNATURES

Protocol Number: KBP-201

Protocol Title: A Phase I/II, First-in-human, Observer-blinded, Randomized, Placebo-controlled, Parallel Group Study to Evaluate the Safety and Immunogenicity of TAP-COVID-19 SARS-CoV-2 Vaccine with CpG Adjuvant in Healthy Adults Aged 18-49 and 50-85

Kentucky BioProcessing, Inc. Signatures

This clinical study protocol has been reviewed and approved by Kentucky BioProcessing, Inc.

DocuSigned by:
Oscar Guzman
20A855B6C6BB461...

11/17/2021

Oscar (Tony) A. Guzman, MD, CP
Clinical Project Lead

Date

Protocol Number: KBP-201

Protocol Title: A Phase I/II, First-in-human, Observer-blinded, Randomized, Placebo-controlled, Parallel Group Study to Evaluate the Safety and Immunogenicity of TAP-COVID-19 SARS-CoV-2 Vaccine with CpG Adjuvant in Healthy Adults Aged 18-49 and 50-85

Investigator Signature

I agree to conduct the aforementioned study according to the terms and conditions of the protocol, GCP guidelines, and all other applicable local and regulatory requirements. All information pertaining to the study will be treated in a confidential manner.

Site Name

Print Name

Signature Date

APPENDIX A DIARY CARD EXAMPLE

Example Diary Card may be adjusted to add additional subject collection information or CRU and/or subject contact information.

VACCINE REACTION AND ADVERSE EVENT DIARY

Section 1: Diary - Reactogenicity Days 1-8

My Subject ID number is _____

Date								
Day of immunization ▶ / **Symptom**	Evening of Dose	1 Day after	2 Days after	3 Days after	4 Days after	5 Days after	6 Days after	7 Days after
Body temperature **Celsius (C) or Fahrenheit (F)**	°	°	°	°	°	°	°	°
Fill in today's column by entering the worst grade/severity for each symptom that you have had in the last day (24 hours). Symptom grades are defined at the bottom of the page.								
No Symptoms of Any Kind – Tick this box								
Generalized Symptoms								
Headache								
Fatigue								
Muscle Pain								
Joint pain								
Nausea								
Chills								
Feverish								
Rash (not at injection site)								
Local Reactions								
Pain								
Erythema / redness in mm								
Induration in mm								
Swelling in mm								
In addition, tick the box in today's column if your answer to the question below is YES.								
Any other new symptom(s)? Y or N. If yes, describe in section 2.								

Grade 0 =	I didn't have it at all.
Grade 1 =	I noticed it, but it didn't interfere with my usual activities at all.
Grade 2 =	I had it, and it was bad enough to prevent a significant part of my usual activities.
Grade 3 =	I had it, and it prevented most or all of my normal activities, or I had to see a doctor for prescription medicine.
Grade 4 =	I had to visit the ER or was hospitalized because of the specific symptom

VACCINE REACTION AND ADVERSE EVENT DIARY

Section 2: Other Adverse Events

Please describe any other symptoms experienced beyond those listed above. Please describe symptom or diagnosis, severity, start and stop day, if you saw a health care professional and severity below.

Symptom or Diagnosis if visited a Health Care Provider	Did you visit a health care provider	Start Date	Stop Date	Severity[1]	Comments, including any medicine prescribed or taken to reduce the symptoms

[1]**Please use these qualitative definitions to grade your symptoms:**	
Grade 1 =	I noticed it, but it didn't interfere with my usual activities at all.
Grade 2 =	I had it, and it was bad enough to prevent a significant part of my usual activities.
Grade 3 =	I had it, and it prevented most or all of my normal activities, or I had to see a doctor for prescription medicine.
Grade 4 =	I had it and visited the ER or was hospitalized for it.

Please return this document to your study site.
If at any time you have questions about completing the diary card, your health, or about the study in general, please contact the study site personnel.

Study Site Contact Information:
Principal Investigator Name:
Study Coordinator/Point of Contact:
Phone #:
Email address:

APPENDIX B POTENTIAL IMMUNE-MEDIATED MEDICAL CONDITIONS

Gastrointestinal Disorders

- Autoimmune pancreatitis
- Celiac disease
- Crohn's disease
- Microscopic colitis
- Ulcerative colitis
- Ulcerative proctitis

Liver Disorders

- Autoimmune cholangitis
- Autoimmune hepatitis
- Primary biliary cirrhosis
- Primary sclerosing cholangitis

Metabolic Diseases

- Addison's disease
- Autoimmune hypophysitis
- Autoimmune thyroiditis (including Hashimoto thyroiditis)
- Diabetes mellitus type I
- Grave's or Basedow's disease

Musculoskeletal Disorders

- Antisynthetase syndrome
- Dermatomyositis
- Juvenile chronic arthritis (including Still's disease)
- Mixed connective tissue disorder
- Polymyalgia rheumatic
- Polymyositis
- Psoriatic arthropathy
- Relapsing polychondritis
- Rheumatoid arthritis
- Scleroderma, including diffuse systemic form and CREST (alcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) syndrome
- Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome), and undifferentiated spondyloarthritis
- Systemic lupus erythematosus
- Systemic sclerosis

Neuroinflammatory Disorders

- Acute disseminated encephalomyelitis, including site-specific variants (eg, noninfectious encephalitis, encephalomyelitis, myelitis, radiculomyelitis)

- Cranial nerve disorders, including paralyses/paresis (eg, Bell's palsy)
- Guillain-Barré syndrome, including Miller Fisher syndrome and other variants
- Immune-mediated peripheral neuropathies and plexopathies, including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy
- Multiple sclerosis
- Narcolepsy
- Optic neuritis
- Transverse myelitis
- Myasthenia gravis, including Eaton-Lambert syndrome

Skin Disorders

- Alopecia areata
- Autoimmune bullous skin diseases, including pemphigus, pemphigoid and dermatitis herpetiformis
- Cutaneous lupus erythematosus
- Erythema nodosum
- Morphoea
- Lichen planus
- Psoriasis
- Sweet's syndrome
- Vitiligo

Vasculitides

- Large vessels vasculitis including: giant cell arteritis such as Takayasu's arteritis and temporal arteritis
- Medium sized and/or small vessels vasculitis including the following:
    - Polyarteritis nodosa
    - Kawasaki's disease
    - Microscopic polyangiitis
    - Wegener' granulomatosis
    - Behcet's syndrome
    - Leukocytoclastic vasculitis
    - Henoch-Schonlein purpura
    - Necrotizing vasculitis and antineutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified)
    - Churg-Strauss syndrome (allergic granulomatous angiitis)
    - Buerger's disease thromboangiitis obliterans

Others

- Antiphospholipid syndrome
- Autoimmune hemolytic anemia

- Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis)
- Autoimmune myocarditis/cardiomyopathy
- Autoimmune neutropenia
- Autoimmune pancytopenia
- Autoimmune thrombocytopenia
- Goodpasture syndrome
- Idiopathic pulmonary fibrosis
- Pernicious anemia
- Polyglandular autoimmune syndrome
- Raynaud's phenomenon
- Sarcoidosis
- Sjögren's syndrome
- Stevens-Johnson syndrome
- Uveitis

APPENDIX C ADDITIONAL ELISA DETAILS

Name That Appears on Laboratory Report	Vendor	SARs-CoV-2 Antigen	Reporting Status	Intended Use
Anti-SARS-CoV-2 IgG Qual	Euroimmun	Spike (S)	Blinded starting at the Day 1 Visit	It is intended for use as an aid in identifying individuals with an adaptive immune response to SARS-CoV-2, indicating recent or prior infection. At this time, it is unknown for how long antibodies persist following infection and if the presence of antibodies confers protective immunity. This test should not be used to diagnose acute SARS-CoV-2 infection.
SARS-CoV-2 IgG Qual	Abbott Architect	Nucleocapsid (N)	Unblinded throughout the duration of the study	This assay is designed to detect immunoglobulin class G (IgG) antibodies to the nucleocapsid protein of SARS-CoV-2 in serum and plasma from individuals who are suspected to have had COVID-19 or in serum and plasma of subject that may have been infected by SARS-CoV-2.
COVID-19 IgM	Epitope Diagnostics	Nucleocapsid (N)	Unblinded throughout the duration of the study	This test is used as an aid for the detection of novel COVID-19.

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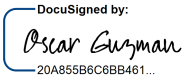
Oscar Guzman guzmano@kentuckybioprocessing.com Kentuchy BioProcesing Security Level: Email, Account Authentication (None)	DocuSigned by:  20A855B6C6BB461... Signature Adoption: Pre-selected Style Using IP Address: 165.225.58.235	Sent: 11/17/2021 9:18:06 AM Viewed: 11/17/2021 9:18:15 AM Signed: 11/17/2021 9:18:34 AM

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Agent Delivery Events	Status	Timestamp

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Certified Delivery Events	Status	Timestamp

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Envelope Sent	Hashed/Encrypted	11/17/2021 9:18:06 AM
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Payment Events	Status	Timestamps

KBP-201 Amendment 8 (Final Protocol v9.0, dated 12 November 2021) Updates in FDA Tabular Format

Protocol Section(s) of Current Version (Final Protocol v9.0, 12 November 2021) Affected by Change	**Previous Version (Final Protocol v8.0, 28 June 2021) Example Text**	**Current Version (Final Protocol v9.0, 12 November 2021) Example Text**	**Rationale**
Synopsis (Objectives, Endpoints, Study Design), Sections 3.1.2, 3.2.2, 4.1, 9.6	Section 9.6 Immunogenicity Analysis The individual sampling and blood collection for ELISA IgG for the spike/anti-RBD and IgM; neutralizing antibody, anti RBD and anti-Fc antibodies will be listed and summarized by time points for each part by treatment.	Section 9.6 Immunogenicity Analysis The individual sampling and blood collection for ELISA analysis to determine IgG and IgM **antibody titers** to the spike RBD and neutralizing antibody **titers for parent (Wuhan) and any variant SARS-CoV-2 strains**, will be listed and summarized by time points for each part by treatment.	Clarification of the antibodies to be used for evaluation of immunogenicity.
Synopsis (Study Design), Section 4.1.2, 5.7.1	5.7.1 Independent Safety Review Committee The iSRC will be asked to review unblinded immunogenicity and safety data when the first 30 subjects vaccinated in the Part A low dose group (including active and placebo subjects) have data available from Day 1 through Day 43 for an assessment of the risk-benefit of the trial. ~~The remaining study cohorts will have an unblinded immunogenicity and safety data review when all subjects in the cohort have data available from Day 1 through Day 43.~~	5.7.1 Independent Safety Review Committee The iSRC will be asked to review unblinded immunogenicity and safety data when the first 30 subjects vaccinated in the Part A low dose group (including active and placebo subjects) have data available from Day 1 through Day 43 for an assessment of the risk-benefit of the trial.	Due to cessation of subject enrollment, the Day 43 iSRC meeting will not be needed for the Part A high dose and Part B subjects.
Sections 4.1.2, 5.7.1, 6.6.2, 6.6.3.2, 9.5	4.1.2 Interim Safety Data Review For the interim analysis, treatment codes will only be unblinded by treatment group (not by individual subjects) and only after the data are deemed ready for the analysis and the data has been monitored. The unblinded review will be completed by the iSRC only and the other team members (~~Sponsor~~, CRO [except for the unblinded team members preparing the data for	4.1.2 Interim Safety Data Review For the interim analysis, treatment codes will be unblinded and only after the data are deemed ready for the analysis and the data has been monitored. The unblinded review will be completed by the iSRC only and the other team members (CRO [except for the unblinded team members preparing the data for unblinded iSRC review], Investigator, and site personnel) will	Since there will be no additional subjects enrolled, the Sponsor will be unblinded to treatment while the remaining study team members remain blinded through the end of the study (~ 1 year).

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	unblinded iSRC review], Investigator, and site personnel) will remain blinded.	remain blinded until completion of the study. **The Sponsor will be unblinded at the interim analysis.**	
Synopsis (Statistical Analysis), Section 9.2	9.2 Analysis Populations Enrolled Population: All subjects who ~~were screened and enrolled to the study. The Enrolled Population will include all screen failures and all subjects who are discontinued from the study prior to study vaccine administration and will be used for disposition summaries.~~ Per Protocol (PP) Population: Includes all subjects in the Safety Population who receive the assigned doses of the study vaccine/placebo according to protocol, have serology results, and have no major protocol deviations affecting the primary immunogenicity outcomes, as determined by the Sponsor before database lock and unblinding. Subjects that are immunized with an approved vaccine will be captured as a subset analysis of the PP Population ~~in six-month increments (Days 90-181 and 181-365)~~ based on the date of receiving an approved COVID-19 vaccine.	9.2 Analysis Populations Enrolled Population: All subjects who **signed the ICF**. Per Protocol (PP) Population: Includes all subjects in the Safety Population who receive the assigned doses of the study vaccine/placebo according to protocol, have serology results, and have no major protocol deviations affecting the primary immunogenicity outcomes, as determined by the Sponsor before database lock and unblinding. Subjects that are immunized with an approved vaccine will be captured as a subset analysis of the PP Population **at Days 181, 273, and 365** based on the date of receiving an approved COVID-19 vaccine.	Updates to the analysis population for consistency with the Statistical Analysis Plan.
Synopsis (Statistical Analysis), Sections 9, 9.6	Section 9.6 Immunogenicity Analysis All derived immunogenicity secondary endpoint parameters: GMT, GMT ratio, GMFR, GMI, and seroconversion rates will be listed and summarized by scheduled time point using descriptive statistics (n, mean, SD, minimum, median,	Section 9.6 Immunogenicity Analysis All derived immunogenicity secondary endpoint parameters: GMT, GMT ratio, GMFR, GMI, and seroconversion rates will be listed and summarized by scheduled time point using descriptive statistics (n, mean, SD, minimum, median, maximum,	Clarification that the immunogenicity secondary endpoint parameters GMT, GMT ratio, GMFR, GMI, and seroconversion rates will need geometric means, CV%, and GeoCV% summarized in addition to the arithmetic mean.

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	maximum, and 95% CI) for each part by treatment. Graphical display of the summary results or at individual time points will be provided as needed.	**geometric mean, CV%, GeoCV%,** and 95% CI) for each part by treatment. Graphical display of the summary results or at individual time points will be provided as needed **(eg, scatter plots of subject titer values to visually display individual data points).**	
Section 9.0	9.0 Statistical Considerations The statistical evaluation will be performed using SAS® software version 9.4 or higher (SAS Institute, Cary, NC). All data will be listed, and summary tables will be provided. No formal significance testing will be performed. Summary statistics will be presented by treatment group.	9.0 Statistical Considerations The statistical evaluation will be performed using SAS® software version 9.4 or higher (SAS Institute, Cary, NC). All data will be listed, and summary tables will be provided. No formal significance testing will be performed. Summary statistics will be presented by treatment group **and include subset analysis (eg, all subjects, seronegative subjects [ie, neutralizing antibody titer < 10 at screening], seropositive subjects, and subjects that received an FDA Emergency Use Authorization/licensed COVID vaccine).**	Addition of the subsets to be analyzed.
Sections 9.6, 9.7, 9.8	9.6 Immunogenicity Analysis In addition, if any subjects seropositive for SARS-CoV-2 are enrolled, safety and efficacy subgroup analysis will be performed for this group of subjects.	9.6 Immunogenicity Analysis **Subjects who are** seropositive **and seronegative at screening will also be summarized** and safety and efficacy subgroup analysis will be performed for **these groups** of subjects. **Additional details for analysis are presented in the SAP.**	Clarification that seropositive and seronegative screening status will be summarized and that safety and efficacy will be analyzed using these subgroups.

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Sections 7.6, 8.2.2	7.6 SARS-CoV-2 Exposure and Asymptomatic Monitoring Subjects will be monitored for SARS-CoV-2 exposure for potential asymptomatic infection throughout the study. CRU staff will interview subjects about any potential exposure to the virus. If a subject has had potential exposure, the CRU will perform an unscheduled nasopharyngeal swab.	7.6 SARS-CoV-2 Exposure and Asymptomatic Monitoring Subjects will be monitored for SARS-CoV-2 exposure for potential asymptomatic infection throughout the study. CRU staff will interview subjects about any potential exposure to the virus. If a subject has had potential exposure, the CRU will perform an unscheduled nasopharyngeal swab. **Subjects will not be discontinued from the study due to positive SARS-CoV-2 test results.**	Reiterate that subjects will not be discontinued due to positive SARS-CoV-2 test.
Section 9.8	9.8 Safety Analysis In addition, if any subjects seropositive for SARS-CoV-2 are enrolled, safety and efficacy subgroup analysis will be performed for this group of subjects.	9.8 Safety Analysis Subjects who are seropositive **and seronegative at screening will also be summarized and** safety and efficacy subgroup analysis will be performed for this group of subjects. **Additional details for safety analysis are presented in the SAP.**	Clarification of analysis of seronegative and seropositive subjects.

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Study Administrative Structure Section 16	Study Administrative Structure Sponsor's Contact: Hugh Haydon President Kentucky BioProcessing, Inc. ELISA (IgM & IgG) and Cell Mediated Immunity Laboratory: ICON Central Laboratory 123 Smith Street Farmingdale, NY 11735 USA	Study Administrative Structure Sponsor's Contact: **Oscar (Tony) A. Guzman, MD, CP** **Clinical Project Lead** Kentucky BioProcessing, Inc. ELISA (IgM & IgG) **Antibody Titer** and Cell Mediated Immunity Laboratories: **VisMederi srl** **Strada del Petriccio e Belriguardo, 35, 53100 Siena, Italia** ICON Central Laboratory 123 Smith Street Farmingdale, NY 11735 USA	Change in Sponsor Contact and protocol signatory and inclusion of the laboratory performing the antibody titers.

Additional updates performed include minor format updates and an update to the protocol version/date.

Clinical Study Protocol

A Phase I/II, First-in-human, Observer-blinded, Randomized, Placebo-controlled, Parallel Group Study to Evaluate the Safety and Immunogenicity of TAP-COVID-19 SARS-CoV-2 Vaccine with CpG Adjuvant in Healthy Adults Aged 18-49 and 50-85

Protocol Number: KBP-201

Version 9.0

Deleted: 8

Date: 12 November 2021

Deleted: 28 June

Sponsor: Kentucky BioProcessing, Inc.
3700 Airpark Drive
Owensboro, KY 42301 USA
Telephone: 270-689-2570

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1 SYNOPSIS

Protocol Title:	A Phase I/II, First-in-human, Observer-blinded, Randomized, Placebo-controlled, Parallel Group Study to Evaluate the Safety and Immunogenicity of TAP-COVID-19 SARS-CoV-2 Vaccine with CpG Adjuvant in Healthy Adults Aged 18-49 and 50-85
Study Phase:	Phase I/II
Objectives:	Primary Objective: • To assess the safety and reactogenicity of two doses of TAP-COVID-19 vaccine with Cytosine PhosphoGuanine (CpG) adjuvant for 7 days post vaccination compared with placebo as determined by solicited local and systemic reactogenicity Secondary Objectives: • To compare the frequency of unsolicited adverse events (AEs) of each dose of TAP-COVID-19 vaccine with CpG adjuvant through Day 43 and serious adverse events (SAEs), medically attended adverse events (MAAEs), new onset chronic diseases (NOCDs), and adverse events of special interest (AESIs) through Day 365 Comparisons include: o High dose (45 µg TAP-COVID-19 vaccine + 0.5 mg CpG) to placebo o Low dose (15 µg TAP-COVID-19 vaccine + 0.5 mg CpG) to placebo o High dose (45 µg TAP-COVID-19 vaccine + 0.5 mg CpG) to low dose (15 µg TAP-COVID-19 vaccine + 0.5 mg CpG) • To evaluate the immunogenicity of TAP-COVID-19 vaccine with CpG adjuvant compared with placebo in terms of antibody assessed by geometric mean titers (GMTs) of both spike receptor binding domain (RBD) IgG and IgM antibodies and neutralizing antibody response, geometric mean fold rise (GMFR) in neutralizing titer from baseline in all treatment groups at Days 8, 22, 29, 43, 90, 181, 273, and 365 relative to baseline Exploratory Objectives: • To assess cellular immunity by measuring the numbers of cytokine producing CD4+ and CD8+ T-cells from peripheral blood mononuclear cells (PBMCs) response to vaccine in all treatment groups at Days 8, 22, 29, 43, 90, 181, 273, and 365 compared to baseline • To assess the immunogenicity of the RBD and Fc component of the vaccine
Endpoints:	Primary Endpoints: Occurrence of Solicited AEs: • Solicited administration site reactions (eg, pain, tenderness, erythema/redness, induration/swelling) during the 7-day follow-up period after each vaccination (Day 1-8 and Day 22-29) • Solicited systemic events (eg, fever, nausea/vomiting, diarrhea, headache, fatigue, myalgia) during the 7-day follow-up period after each vaccination (Day 1-8 and Day 22-29) Secondary Endpoints: Safety: • Unsolicited AEs, MAAEs, and AESIs up to Day 43 • SAEs, MAAEs, NOCDs, and AESIs up to Day 365 (approximately 1 year after first vaccination) Immunogenicity: Vaccine enzyme-linked immunosorbent assay of both spike receptor binding domain (RBD) IgG and IgM antibodies and neutralizing antibody titers for each treatment group: • GMT at baseline and Days 15, 22, 43, 90, 181, 273, and 365 • GMT ratio ($GMT_{placebo}/GMT_{TAP\text{-}COVID\text{-}19}$) at baseline and Days 22, 29, 43, 90, 181, 273,

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	and 365 • GMFR at Days 8, 22, 29, 43, 90, 181, 273, and 365 relative to baseline • Seroconversion rates on Days 8, 15, 22, 29, 43, 90, 181, 273, and 365. Seroconversion is defined as the proportion of subjects at the respective time point that have detectable antibodies (IgG and IgM) against SARS-CoV-2 Spike Protein RBD following challenge with vaccine (and potentially by natural asymptomatic or symptomatic infection by the virus in case of a placebo subject). • Geometric mean increase (GMI) on Days 8, 22, 29, 43, 90, 181, 273, and 365 Exploratory Endpoints: Cellular immunity: • The number of cytokine producing CD4+ and CD8+ T-cells from PBMCs responsive to vaccine antigens in all treatment groups on Days 8, 22, 29, 43, 90, 181, 273, and 365 compared to baseline Immunogenicity: • Anti-RBD and anti-Fc antibodies at baseline and Days 8, 15, 22, 29, 43, 90, 181, 273, and 365
Study Design:	This is a first-in-human (FIH), observer-blinded, randomized, placebo-controlled, parallel group study to evaluate the safety and immunogenicity of TAP-COVID-19 vaccine with CpG adjuvant in healthy adult subjects in 2 age groups, Part A (18-49 years) and Part B (50-85 years). A study schematic is presented in Figure 4-1. PART A and PART B: Subjects will be screened up to 14 days (Day -14 to Day -1) before randomization. Overall, approximately 90 eligible healthy adults ages 18-49 years (inclusive) will be enrolled for Part A and 90 eligible healthy adults ages 50-85 years will be enrolled for Part B. Sentinel dosing will be utilized in this FIH study. Sentinel cohorts will be used for the following groups: - Part A (18-49 years) low dose (15 µg TAP-COVID-19 vaccine + 0.5 mg CpG) - Part B (50-85 years) low dose (15 µg TAP-COVID-19 vaccine + 0.5 mg CpG) - Part A (18-49 years) high dose (45 µg TAP-COVID-19 vaccine + 0.5 mg CpG) - Part B (50-85 years) high dose (45 µg TAP-COVID-19 vaccine + 0.5 mg CpG) Three sentinel subjects from each part will be randomized 2:1 (active:placebo). The independent Safety Review Committee (iSRC) will review the safety and tolerability data for the sentinel subjects through Day 8 prior to enrollment of the remaining cohort subjects randomized 2:1 (active:placebo). When all subjects in Part A (18-49 years) low dose have received the first vaccination and have all safety data through Day 8, the iSRC will convene and review the safety data to ensure that there are no safety concerns and that none of the Study Halting Rules have been met before recommending that the study enroll Part A high dose and Part B (50-85 years) low dose. When all subjects in Part B (50-85 years) low dose have received the first vaccination and have all safety data through Day 8, the iSRC will convene and review the safety data to ensure that there are no safety concerns and that none of the Study Halting Rules have been met before recommending that the study enroll Part B high dose. The iSRC will convene and review the safety data when a minimum of 23 subjects have completed Day 29 after the second vaccination for Part A (low and high dose) and for Part B (low and high dose) to ensure that there are no concerns. Both Part A (18-49 years) and Part B (50-85 years) will be randomized in a 2:1 ratio (active:placebo) for each treatment dose (15 µg and 45 µg TAP-COVID-19 vaccine + 0.5 mg CpG) for a total of 90 subjects per Part (30 subjects 15 µg TAP-COVID-19 vaccine + 0.5 mg CpG:30 subjects 45 µg TAP-COVID-19 vaccine + 0.5 mg CpG:30 subjects placebo). Treatment A: TAP-COVID-19 vaccine (15 µg) + CpG (0.5 mg) intramuscular (IM) injection

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	on Day 1 and Day 22 (±3 days) Treatment B: TAP-COVID-19 vaccine (45 µg) + CpG (0.5 mg) IM injection on Day 1 and Day 22 (±3 days) Treatment C: Placebo (buffered saline solution) IM injection on Day 1 and Day 2 (±3 days) Study vaccine will be prepared by an unblinded site pharmacist and administered at the clinical research site on Day 1 and Day 22 (±3 days) by unblinded clinical research unit (CRU) personnel. Subjects will be observed for immediate AEs and/or reactogenicity for approximately 60 minutes after administration of vaccine. Subjects will be provided with a Diary Card and will be trained to record specifically elicited systemic and local symptoms daily as well as any additional AEs during the 7-day follow-up period after each vaccination. Visits will be conducted at the clinical site on an outpatient basis or as a telephone visit per the Schedule of Assessments and Procedures. Subjects will participate in the study for approximately 1 year from the first dose. AEs and concomitant medications will be captured through Day 43. Blood and serum samples for safety laboratory tests, RBD IgG and IgM antibodies and neutralizing antibody titers, cell-mediated immunity, and other future biomedical research will be obtained at baseline and before administration of vaccine dose 2 and after each vaccination per the Schedule of Assessments and Procedures. SAEs, MAAEs, NOCDs, and AESIs only will be captured after Day 43 to study completion (Day 365 [approximately 1 year after first vaccination]). Prior to receiving a second dose of vaccine, subjects will have the following assessments performed to ensure eligibility: vital signs (including temperature), review of clinical laboratory test results to date, nasopharyngeal swab Day 15 to check for SARS-CoV-2 infection (reverse transcription polymerase chain reaction [RT-PCR] result must be received by the CRU and negative prior to the second vaccine administration), medical history since last visit including AE assessment for SAEs, Grade 3 AEs, or AESIs that are possibly, probably, or definitely related to study vaccine without a plausible alternative explanation, targeted physical examination, recheck of eligibility criteria, and pregnancy test (as applicable). Subjects will be monitored for SARS-CoV-2 exposure for potential asymptomatic infection throughout the study. • If a subject has a positive or borderline ELISA anti-N IgG result, sites should have the subject return for an unscheduled PCR. If the ELISA is positive and the PCR is negative, the sites should follow the subjects using the standard of care under Investigator discretion, retesting ELISA at the next study visit(s) or sooner (per the Investigator's decision). • If the subject has a positive or borderline ELISA anti-N IgG AND a positive PCR test, the clinical sites should bring the subjects back for repeat PCR testing as described below. • The clinical sites should continue to collect PCR tests if a subject is experiencing possible COVID-19 symptoms, or had possible exposure to SARS-CoV-2 (ie, close contact tests positive for SARS-CoV-2). Testing will occur every 2 weeks for a total of 4 weeks (if 2 consecutive negative tests) or until negative (x2) after a positive result. Positive results will be reported as an AESI and subjects followed for disease severity, duration, and outcome. Subjects who are seropositive for SARS-CoV-2 and asymptomatic will be allowed to enroll into Parts A and B of the study as long as the subject is RT-PCR negative. Interim Safety Data Reviews: For all of the sentinel groups, the iSRC will meet to review the sentinel subjects' safety and tolerability data through Day 8. In the event that iSRC has not met for the post Day 8 review because the entire sentinel group (n = 3) has not completed Day 8 before a sentinel subject

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	is to receive the second vaccine on Day 22, the iSRC will meet on an ad hoc basis, to ensure there are no safety concerns and that none of the Individual Discontinuation Criteria or Study Halting Rules have been met, prior to the sentinel subjects receiving the second vaccine. When all subjects in Part A (18-49 years) low dose have received the first vaccination and have all safety data through Day 8, the iSRC will convene and review the safety data to ensure that there are no safety concerns and that none of the Study Halting Rules have been met before recommending that the study enroll Part A high dose and Part B low dose. The same strategy will be used for Part B when going from low to high dose. The iSRC will be asked to review unblinded immunogenicity and safety data when the first 30 subjects vaccinated in the Part A low dose group (including active and placebo subjects) have data available from Day 1 through Day 43 for an assessment of the risk-benefit of the trial. The iSRC will also meet when a minimum of 23 subjects have completed Day 29 after the second vaccination for Part A (low and high dose) and for Part B (low and high dose) to review safety data to ensure that there are no concerns. The iSRC will also review all data through Day 43 for Part A and for Part B in both dose groups to monitor for ongoing safety concerns and immunogenicity analysis. When the Parts A and B Day 43 (low and high dose) review is complete, the iSRC will recommend a dose for the Part C Expansion (optional). Progression to Part C will only take place after the Center for Biologics Evaluation and Research (CBER) has had the opportunity to review the Day 43 data from Parts A and B and concurs with the plan to proceed with enrollment. Study Halting Rules: The occurrence and confirmation of 1 or more of the following findings will result in suspension of further enrollment and study vaccine administration pending urgent review (within 1 week) of the safety data by the iSRC. Subjects who are withdrawn from study vaccine (if applicable) will continue to be monitored for safety and immunogenicity. • One or more subjects experience an SAE assessed as possibly related, probably related, or related to study vaccine without a plausible alternative explanation. • One or more subjects have generalized urticaria during the 7-day post vaccination period. • One or more subjects develop a Grade 4 local reaction for which there is no alternative plausible explanation. • One or more subjects experience laryngospasm, bronchospasm, or anaphylaxis after vaccine administration considered related to the vaccine. • One or more subjects develop a fever >40°C/104°F during the 7 days post vaccination period that is assessed as possibly related, probably related, or related to study vaccine without a plausible alternative explanation. • Two or more subjects within an individual treatment group, or 2 or more subjects across treatment groups, experience any Grade 3 or higher abnormality in the same laboratory parameter determined by the Investigator or medical monitor as clinically significant and that are assessed as possibly related, probably related, or related to study vaccine without a plausible alternative explanation. • Two or more subjects across treatment groups experience a Grade 3 or higher AE, MAAE, or AESI of the same or similar preferred terms (as categorized by the Medical Dictionary for Regulatory Activities [MedDRA]) assessed as possibly related, probably related, or related to study vaccine without a plausible alternative explanation. • Any subject with severe SARS-CoV-2 infection will be assessed for the possibility of vaccine-associated enhanced respiratory disease. Severe SARS-CoV-2 infection is defined as individuals who have virologically confirmed SARS-CoV-2 infection with any of the following: o Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 breaths per minute, heart rate ≥ 125 bpm, oxygen saturation (SpO_2) ≤ 93% on room

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	air at sea level or partial pressure of oxygen/ fraction of inspired oxygen (PaO_2/FiO_2) < 300 mmHg) o Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation [ECMO]) o Evidence of shock (systolic blood pressure < 90 mmHg, diastolic blood pressure < 60 mmHg, or requiring vasopressors) o Significant acute renal, hepatic, or neurologic dysfunction o Admission to an intensive care unit (ICU) o Death due to SARS-CoV-2 infection The iSRC will review unblinded safety data for any subject who dies, requires ICU admission due to SARS-CoV-2 infection, develops an AESI of autoimmune disease or potential immune-medicated medical condition, or experiences vaccine-associated enhanced respiratory disease. If the subject had received TAP-COVID-19, the iSRC may decide whether a study halt for vaccine-enhanced disease is required based on a review of all available clinical and preclinical safety and immunogenicity data.
	PART C EXPANSION (OPTIONAL): The Part C Expansion may be conducted to confirm the safety and immunogenicity of a selected dose across the broad target age span using a larger sample size. The proposed sample size was selected based on World Health Organization (WHO) guidelines on clinical evaluation of vaccines: regulatory expectations Annex I (2001), which states that approximately 300 subjects are needed to identify common local reactogenicity events. A larger sample size will assist in a better characterization of kinetics and range of immunity (neutralizing antibody titers) and provide a more reliable output of seropositivity and seroconversion to TAP-COVID-19 immunization. With the limited clinical experience with SARS-CoV-2 vaccines and the current lack of a biomarker correlate of protection, the generation of this larger data set is relevant to inform the design and implementation of a Phase 3 program. After review of safety and immunogenicity data from Parts A and B through Day 43, a dose for the Phase II expansion study will be recommended by the iSRC. Progression to Part C will only take place after CBER has had the opportunity to review the human clinical plus additional nonclinical data and concurs with the plan to proceed with enrollment. Subjects ≥18 years of age will be enrolled and randomized 1:1 (selected active dose:placebo). Up to 1000 subjects will be enrolled at the chosen dose to provide expanded dose confirmation, safety, and immunogenicity data. Although all subjects in Part C will have safety laboratory tests performed at screening, only the first 200 subjects in Part C will have safety laboratory tests performed at all post-dose time points. The remaining subjects in Part C will not have safety laboratory tests performed at any of the post-dose time points unless the Investigator deems it necessary. Subjects who are seropositive for SARS-CoV-2 and asymptomatic will be allowed to enroll into Part C of the study.
Study Rationale:	Multiple vaccines have been approved for emergency use for the prevention of SARS-CoV-2, with other vaccines close to being available either through emergency use or licensed vaccines. Although work continues on antiviral treatments for SARS-CoV-2, given the crisis of COVID-19 infections in the world, the fast expansion to the United States and other parts of the world, and the global push to vaccinate everyone, additional sources of effective vaccine will be needed.
Subject Selection Criteria:	Inclusion Criteria: Subjects must meet all inclusion criteria to be eligible for study participation. In addition, racial and ethnic minorities will be sought to obtain a diverse study population. ***All Subjects*** 1. Subject read, understood, and signed the informed consent form (ICF). 2. Healthy adult males and females 18-49 years of age (Part A) or 50-85 years of age (Part B), inclusive, at screening.

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3. RT-PCR negative at time of screening
4. Body mass index (BMI) of ≥ 18 and ≤ 30 kg/m^2 at screening. BMI = weight (kg)/(height [m])^2.
5. Must be in general good health before study participation with no clinically relevant abnormalities that could interfere with study assessments.
6. Women of childbearing potential (WOCBP) and men whose sexual partners are WOCBP must be able and willing to use at least 1 highly effective method of contraception (ie, include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy, hormonal oral [in combination with male condoms with spermicide], transdermal, implant, or injection, barrier [ie, condom, diaphragm with spermicide]; intrauterine device; vasectomized partner [6 months minimum], clinically sterile partner; or abstinence) during the study.
   - A female subject is considered to be a WOCBP after menarche and until she is in a postmenopausal state for 12 consecutive months (without an alternative medical cause) or otherwise permanently sterile.
   - Note: Subjects not of childbearing potential are not required to use any other forms of contraception during the study. Non-childbearing potential is defined as subject confirmed:
     - Surgical sterilization (eg, bilateral oophorectomy, bilateral salpingectomy, bilateral occlusion by cautery [Essure System is not acceptable], hysterectomy, or tubal ligation).
     - Postmenopausal (defined as permanent cessation of menstruation for at least 12 consecutive months prior to screening) with follicle-stimulating hormone ≥ 30 mIU/mL at screening.
7. WOCBP must have a negative urine pregnancy test before each vaccination.
8. Must be able to attend all visits, including unscheduled visits if respiratory symptoms suggestive of SARS-CoV-2 infection develop during the study, for the duration of the study and comply with all study procedures, including daily completion of the Diary Card for 7 days after each injection.

Exclusion Criteria:

Subjects will not be eligible for study participation if they meet any of the exclusion criteria, or will be discontinued at the discretion of the Investigator if they develop any of the exclusion criteria during the study.

Parts A and B

1. History of an acute or chronic medical condition including dementia that, in the opinion of the Investigator, would render vaccination unsafe or would interfere with the evaluation of responses. Chronic conditions that are NOT included on the Center for Disease Control's list of subjects at higher risk for severe illness from SARS-CoV-2 are acceptable if the condition has been stable for the 3 months prior to vaccine administration (Day 1), with no medication changes, and no hospitalization in the past 6 months.
2. History of any medical conditions that place subjects at higher risk for severe illness due to SARS-CoV-2 including but not limited to cancer, chronic kidney disease at any stage, chronic lung disease, dementia or other neurological conditions, diabetes (Type 1 or Type 2), Down syndrome, heart conditions, human immunodeficiency virus (HIV) infection, immunocompromised state (weakened immune system), liver disease, overweight/obesity, pregnancy, sickle cell disease or thalassemia, smoker (current or former), transplants (solid organ or blood stem cell), stroke or cerebrovascular disease, and substance use disorders.
3. History of ongoing clinical condition or medication or treatments that may adversely affect the immune system.

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	4. Individuals who are RT-PCR positive for SARS-CoV-2 at screening or prior to second dose of TAP-COVID-19 vaccine. 5. Individuals who are at increased risk of exposure to SARS-CoV-2 (eg, healthcare workers, emergency responders). 6. Close contact of anyone known to have SARS-CoV-2 infection within 30 days prior to vaccine administration. 7. Living in a group care facility (eg, assisted living or nursing home). 8. Individuals with any elevated (Grade 1 or higher) laboratory test assessed as clinically significant for age by the Investigator at screening. 9. Individuals with elevated (Grade 1 or higher) liver function enzyme at screening, may repeat testing once to re-assess clinical significance. If the retest comes back within normal range, the subject will be eligible for enrollment with Investigator and Medical Monitor approval. See below for the criteria for excluding subjects with elevated liver enzymes (once confirmed by retest): • Alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), or gamma-glutamyl transferase (GGT) >1.5 × upper limit of normal (ULN) • Total bilirubin >1.6 × ULN 10. Active neoplastic disease (excluding nonmelanoma skin cancer that was successfully treated) or a history of any hematological malignancy. "Active" is defined as having received treatment within the past 5 years. 11. Long-term (greater than 2 weeks) use of oral or parenteral steroids, high-dose inhaled steroids (>800 µg/day of beclomethasone dipropionate or equivalent), or immunomodulatory drugs within 6 months before screening (nasal and topical steroids are allowed). 12. History of autoimmune, inflammatory disease, or potential immune-mediated medical conditions (Appendix B). 13. Women currently pregnant, lactating, or planning a pregnancy between enrollment and 181 days after randomization. 14. History of Guillain-Barré Syndrome. 15. History of anaphylactic-type reaction to injected vaccines. 16. Known or suspected hypersensitivity to 1 or more of the components of the vaccine, including thimerosal, tobacco, and CpG adjuvant. 17. History of alcohol abuse, illicit drug use, physical dependence to any opioid, or any history of drug abuse or addiction within 12 months of screening. Note: In those regions where cannabis use is legal, it will be left to the discretion of the Investigator to decide if a subject is an occasional user or an abuser of cannabis. The Investigator should discuss user/abuser status on a case-by-case basis with the Medical Monitor prior to enrollment. 18. Acute illness or fever within 3 days before study enrollment (enrollment may be delayed for full recovery if acceptable to the Investigator). 19. Individuals currently participating or planning to participate in a study that involves an experimental agent (vaccine, drug, biologic, device, or medication); or who have received an experimental agent within 1 month (3 months for immunoglobulins) before enrollment in this study; or who expect to receive another experimental agent during participation in this study. 20. Receipt of immunoglobulin or another blood product within the 3 months before enrollment in this study or those who expect to receive immunoglobulin or another blood product during this study. 21. Individuals who intend to donate blood within 6 months after the first vaccination. 22. Individuals using prescription medications for prophylaxis of SARS-CoV-2.

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	23. Individuals who plan to receive another vaccine within the first 3 months of the study except influenza vaccine which should not be given within 2 weeks of study vaccine. 24. Receipt of any other approved SARS-CoV-2 vaccine prior to the first study vaccine or within 90 days after administration of the first study vaccine. 25. Receipt of any other experimental coronavirus vaccine at any time prior to or during the study. 26. Receipt of any investigational vaccine or drug within 1 month of enrollment and through the end of the study (1 year after first vaccination). 27. Plan to travel outside the subjects' country of residence from enrollment through Day 43. 28. History of surgery or major trauma within 12 weeks of screening, or surgery planned during the study. 29. Significant blood loss (>450 mL) or has donated 1 or more units of blood or plasma within 6 weeks prior to study participation. 30. Strenuous activity (as assessed by the Investigator) within 48 hours prior to dosing (Days 1 and 22). 31. A positive urine drug screen without evidence of corresponding prescribed concomitant medication(s) at Screening. Note: A positive drug screen result with a corresponding prescribed concomitant medication will be allowed if, in the opinion of the investigator and Medical Monitor, the concomitant medication does not make the subject unsuitable to participate in the clinical trial. For a positive tetrahydrocannabinol result, refer to Exclusion Criteria #17. 32. Positive alcohol screen. 33. Positive screen for HIV-1 and HIV-2 antibodies, hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV) antibody. 34. Involved in the planning or conduct of this study. 35. Unwilling or unlikely to comply with the requirements of the study. 36. Subject is an employee, contractor, friend of or relative of any employee of Sponsor, contract research organization (CRO), study site or site affiliate. ***Part C*** If the study proceeds to the Part C Expansion study, the following exclusion criteria (Number, from Parts A and B) will be not applicable. (5) Individuals who are at increased risk of exposure to SARS-CoV-2 (eg, healthcare workers, emergency responders). (6) Close contact of anyone known to have SARS-CoV-2 infection within 30 days prior to vaccine administration. (7) Living in a group care facility (eg, assisted living or nursing home). (31) A positive urine drug screen without evidence of corresponding prescribed concomitant medication(s) at Screening. Note: A positive drug screen result with a corresponding prescribed concomitant medication will be allowed if, in the opinion of the investigator and Medical Monitor, the concomitant medication does not make the subject unsuitable to participate in the clinical trial. (32) Positive alcohol screen. (33) Positive screen for HIV-1 and HIV-2 antibodies, HBsAg, or HCV antibody (Parts A and B). For Part C, subjects known to be HIV positive or have active Hepatitis B or C infection will be excluded.
Study Vaccine, Dose, and Route of Administration:	TAP-COVID-19: 0.5 mL of TAP-COVID-19 vaccine at 15 µg or 45 µg + CpG (0.5 mg), administered by IM injection on Day 1 and Day 22 (±3 days).

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Reference Vaccine, Dose and Route of Administration:	Placebo: 0.5 mL buffered saline solution, administered by IM injection on Day 1 and Day 22 (±3 days).
Planned Sample Size:	No formal sample size calculation was performed. A total of 180 subjects will be enrolled in Parts A and B. Approximately 90 eligible subjects (aged 18-49 years), with 30 subjects per treatment group for Part A and 90 eligible subjects (aged 50-85 years), with 30 subjects per treatment for Part B, will be enrolled in the study. An optional Part C Expansion may be conducted to confirm the safety and immunogenicity of the selected dose of vaccine in up to 1000 adult subjects randomized 1:1 (single dose level of study vaccine:placebo). The proposed sample size was selected based on WHO guidelines on clinical evaluation of vaccines: regulatory expectations Annex I (2001), which states that approximately 300 subjects are needed to identify common local reactogenicity events. A larger sample size will assist in a better characterization of kinetics and range of immunity (neutralizing antibody titers) and provide a more reliable output of seropositivity and seroconversion to TAP-COVID-19 immunization. With the limited clinical experience with SARS-CoV-2 vaccines and the current lack of a biomarker correlate of protection, the generation of this larger data set is relevant to inform the design and implementation of a Phase 3 program.
Statistical Analysis:	Analysis Populations: Enrolled Population: All subjects who signed the ICF. Safety Population: All subjects who provided consent, are randomized, and received any amount of study vaccine/placebo. The Safety Population will be used for the demographic, baseline characteristic, safety data summaries, and the analysis of primary endpoints such as occurrence of solicited local and systemic reactogenicity. Per Protocol (PP) Population: Includes all subjects in the Safety Population who receive the assigned doses of the study vaccine/placebo according to protocol, have serology results, and have no major protocol deviations affecting the primary immunogenicity outcomes, as determined by the Sponsor before database lock and unblinding. Subjects that are immunized with an approved vaccine will be captured as a subset analysis of the PP Population at Days 90, 181, 273, and 365 based on the date of receiving an approved COVID-19 vaccine. Modified Intent-to-Treat (mITT) Population: Includes all subjects in the Safety Population who provide any serology data. The mITT Population will be used for immunogenicity analysis. Immunogenicity Analysis: The mITT Population will be used for all listings and summary statistics corresponding to immunogenicity analysis. The individual sampling and blood collection for ELISA analysis to determine IgG and IgM antibody titers to the spike RBD and neutralizing antibody titers for parent (Wuhan) and any variant SARS-CoV-2 strains, will be listed and summarized by time points for each part by treatment. All derived immunogenicity secondary endpoint parameters: GMT, GMT ratio, GMFR, GMI, and seroconversion rates will be listed and summarized by scheduled time point using descriptive statistics (n, mean, standard deviation, minimum, median, maximum, geometric mean, coefficient of variation (percentage) (CV%), geometric coefficient of variation (percentage) (GeoCV%), and 95% confidence interval) for each part by treatment. PBMC and serum sample data for future research results at each scheduled visit will also be provided separately in a listing and summary table, if applicable. Graphical display of the summary results or at individual time points will be provided as needed (eg, scatter plots of subject titer values to visually display individual data points).

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	Cellular Analysis: The number of IFN-γ and IL-5 producing T-cells (CD4+ and CD8+) from PBMCs responsive to vaccine antigens will be listed and summarized by time point using appropriate descriptive statistics for each part by treatment. Safety Analysis: Safety Population will be used for all safety variables specified. All safety data will be summarized by part and treatment. No statistical tests will be performed. In addition, if any subjects seropositive for SARS-CoV-2 are enrolled, safety and efficacy subgroup analysis will be performed for this group of subjects.

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1.1 Schedule of Assessments and Procedures

Table 1-1 Schedule of Assessments and Procedures

Study Visit	SCR	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13 Study End	UNSCH /ET
Study Day (Visit Window) / Procedures	Day -14 to Day -1	Day 1	Day 8 (±1 Day)	Day 15 (±1 Day)	Day 22 (±3 Days)	Day 29 (±2 Days)	Day 43 (±2 Days)	Day 76 (±3 Days)	Day 90 (±14 Days)	Day 120 (±3 Days)	Day 150 (±3 Days)	Day 181 (±14 Days)	Day 273 (±14 Days)	Day 365 (±14 Days)	
Informed consent	X														
Eligibility	X	X			X										
Medical history	X	X [a]	X [a]	X [a]	X [a]	X [a]	X [a]		X [a]			X [a]	X [a]	X [a]	X [a]
Demographic and baseline characteristics [b]	X														
Complete physical examination	X														
Targeted physical examination [c]		X	X	X	X	X	X					X			X
Height, weight, BMI	X														
Vital sign measurements [d]	X	X [d]	X	X	X [d]	X	X		X			X	X	X	X
Urine pregnancy test [e]	X	X			X										
Urine drug screen [f]	X														
HIV-1/2, HBsAg, HCV [g]	X														
Nasopharyngeal swab for RT-PCR [h]	X			X											X
Serostatus (IgM & IgG) for SARS-CoV-2 [q]	X														
Oral Temperature (pre-vaccination)		X			X										

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Study Visit	SCR	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13 Study End	UNSCH /ET
Study Day (Visit Window) / Procedures	Day -14 to Day -1	Day 1	Day 8 (±1 Day)	Day 15 (±1 Day)	Day 22 (±3 Days)	Day 29 (±2 Days)	Day 43 (±2 Days)	Day 76 (±3 Days)	Day 90 (±14 Days)	Day 120 (±3 Days)	Day 150 (±3 Days)	Day 181 (±14 Days)	Day 273 (±14 Days)	Day 365 (±14 Days)	
Vaccination dose (IM)		X			X										
60 minute post-vaccination monitoring (arm check, VS, and targeted PE if general symptoms present)		X			X										
Distribution and training on Diary Card completion		X			X										
Review of Diary Card [i]			X			X									
Telephone visit [j]								X		X	X				
SARS-Cov-2 exposure and asymptomatic monitoring [k]	→	→	→	→	→	→	→	→	→	→	→	→	→	→	
Adverse events [l]		→	→	→	→	→	→								X
SAEs, MAAEs, NOCDs and AESIs [m]		→	→	→	→	→	→	→	→	→	→	→	→	→	X
Prior and concomitant medications [n]	→	→	→	→	→	→	→								X
Clinical safety laboratory tests [o]	X		X	X	X		X					X			X
Blood collection for ELISA IgM and IgG total antibodies [p]	X		X	X	X	X	X		X			X	X	X	X

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Study Visit	SCR	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13 Study End	UNSCH /ET
Study Day (Visit Window) / Procedures	Day -14 to Day -1	Day 1	Day 8 (±1 Day)	Day 15 (±1 Day)	Day 22 (±3 Days)	Day 29 (±2 Days)	Day 43 (±2 Days)	Day 76 (±3 Days)	Day 90 (±14 Days)	Day 120 (±3 Days)	Day 150 (±3 Days)	Day 181 (±14 Days)	Day 273 (±14 Days)	Day 365 (±14 Days)	
Blood collection for neutralizing, anti-RBD, and anti-Fc antibodies	X		X	X	X	X	X		X			X	X	X	X
Cell-mediated immunity (PBMC)	X		X		X	X	X		X			X	X	X	X
PBMC and serum sample collection for future research	X		X		X	X	X		X			X	X	X	X

Abbreviations: AE = adverse event; AESI = adverse event of special interest; BMI = body mass index; CRU = clinical research unit; ELISA = enzyme-linked immunosorbent assay; ET = Early Termination visit; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; Ig = immunoglobulin; IM = intramuscular; MAAE = medically attended adverse event; NOCD = new-onset chronic disease; PBMC = peripheral blood mononuclear cells; PE = physical examination; RBD = receptor binding domain; RT-PCR = reverse transcription polymerase chain reaction; SAE = serious adverse event; SCR = Screening visit; UNSCH = Unscheduled visit; VS = vital signs

a. Medical history will be collected to determine if any changes have occurred since last visit.

b. Baseline characteristics include tobacco use and history.

c. Post vaccination targeted physical examination includes evaluation of any system indicated by an AE complaint.

d. Pre-dose and approximately 60 minutes post vaccination. Vital signs will be measured after the subject has been resting quietly in a seated position for at least 5 minutes. Vital signs measurements will include blood pressure, heart rate, respiratory rate, and oral temperature.

e. A negative urine pregnancy test must be documented before vaccination on Day 1 and Day 22 for women of childbearing potential. A serum pregnancy test must be performed to confirm any positive urine pregnancy test.

f. For Parts A and B, a positive urine drug screen without evidence of corresponding prescribed concomitant medication(s) at Screening is exclusionary. A positive drug screen result with a corresponding prescribed concomitant medication will be allowed if, in the opinion of the Investigator and Medical Monitor, the concomitant medication does not make the subject unsuitable to participate in the clinical trial.

g. Not performed for Part C.

h. Serial nasopharyngeal swabs (RT-PCR) will be performed on subjects that report either potential exposure to SARS-CoV-2 (ie, close contact tests positive for SARS-CoV-2) or symptoms of SARS-CoV-2 infection. Testing will occur every 2 weeks for a total of 4 weeks (if 2 consecutive negative tests) or until negative after a positive result. Positive results will be reported as an AESI (Section 8.2.2) and subjects followed for disease severity, duration, and outcome.

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i. Review of Diary Card (Appendix A) will include a check that the Diary Card has been completed appropriately and re-training the subjects, if necessary. Any illogical entries will be queried by the site and corrected if appropriate.

j. During telephone visits, CRU staff will interview the subjects about any potential exposure to the virus. If a subject has had potential exposure, the CRU will ask the subject to come in for an unscheduled visit which will include a nasopharyngeal swab. Subjects will be reminded to contact the clinical site any time there is potential exposure to SARS-CoV-2.

k. Subjects will be monitored for SARS-CoV-2 exposure for potential asymptomatic infection throughout the study. CRU staff will interview subjects about any potential exposure to the virus. If a subject has had potential exposure, the CRU will perform an unscheduled nasopharyngeal swab.

l. Adverse events include questioning regarding the specifically elicited events on the Diary Card and complaints spontaneously reported in response to nondirective questions.

m. SAEs, MAAEs, NOCDs, and AESIs will be collected from Day 1 through Day 365/approximately 1 year after first vaccination.

n. Includes all medications taken during the first 43 days of the study, including those started 30 days before and ongoing at vaccination.

o. Refer to Table 7-1 for a detailed list of clinical laboratory test parameters. Clinical laboratory tests can be repeated once at screening to confirm an out-of-range result. If Part C Expansion (optional) is performed, safety laboratory tests will be performed at screening for all Part C subjects in order to satisfy the inclusion/exclusion criteria. In addition, the first 200 subject in Part C will have safety laboratory tests performed at all time points. The remaining subjects in Part C will not have safety laboratory tests performed at any of the post-dose time points unless the Investigator deems it necessary.

p. Subjects with positive ELISA anti-N IgG results without COVID-19 symptoms may indicate asymptomatic SARS-CoV-2 infection and will be followed appropriately. Subjects with a positive ELISA anti-N IgG result should have a PCR test and be followed until both are negative as in the protocol instructions (Section 7.6).

q. Serostatus will not be used to determine eligibility; however, subjects with a positive serostatus for SARS-CoV-2 will have safety and efficacy subgroup analysis performed.

NOTE: In the event multiple post-dose procedures are required to be conducted at the same nominal time point, the timing of antibody titer and cellular immunity blood sample collections will take priority over all other scheduled activities. In practice, the following order is recommended: (1) vital signs measurements; (2) antibody titer and cellular immunity blood sampling; (3) clinical laboratory tests sampling; (4) physical examination and height and body weight measurements. Vital signs may be conducted up to 10 minutes, prior to the nominal time to minimize the potential autonomic effects of blood draws on these measurements and remaining assessments (eg, clinical laboratory tests sampling, physical examination, and height and body weight measurements) may be performed after the nominal time point.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACE-2	angiotensin converting enzyme 2
ADE	antibody-mediated disease enhancement
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
BMI	body mass index
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CD4+	white blood cell T helper cell subtype
CD8+	white blood cell T cytotoxic cell subtype
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practice
CI	confidence interval
CoV	coronavirus
CpG	Cytosine PhosphoGuanine
CPMP	Committee for Proprietary Medicinal Products
CRA	clinical research associate
CRU	clinical research unit
CRO	contract research organization
CSR	clinical study report
CV%	coefficient of variation (percentage)
DAIDS	Division of AIDS
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
EOS	end-of-study
FcγRII	Fc gamma region II of IgG
FDA	Food and Drug Administration
FIH	first-in-human
FiO_2	fraction of inspired oxygen
FSH	follicle-stimulating hormone
GeoCV%	geometric coefficient of variation (percentage)
GGT	gamma-glutamyl transferase
GMFR	geometric mean fold rise
GMI	geometric mean increase
GMT	geometric mean titer
H1N1	influenza A virus subtype H1N1
H3N2	influenza A virus subtype H3N2

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Abbreviation	Definition
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
ICD	International Classification of Diseases
ICF	informed consent form
ICU	intensive care unit
Ig	immunoglobulin
IL	interleukin
IM	intramuscular
IRB	institutional review board
IFN-γ	interferon gamma
iSRC	independent safety review committee
KBP	Kentucky BioProcessing, Inc.
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East Respiratory Syndrome coronavirus
mITT	Modified Intent-to-Treat Population
NOCD	new onset chronic disease
PaO_2	partial pressure of oxygen
PBMC	peripheral blood mononuclear cell
PE	physical examination
PP	Per Protocol
RBD	receptor binding domain
RBD-Fc	fusion protein containing RBD fused to the Fc domain of a human IgG1
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOP	standard operating procedure
SpO_2	oxygen saturation
SRM	study reference manual
SSP	study-specific procedure
TAP	Tobacco Mosaic Virus Antigen Presentation
TAP-COVID-19	Tobacco Mosaic Virus Antigen Presentation SARS-CoV-2 virus Receptor Binding Domain fused to Fc Domain
TEAE	treatment-emergent adverse event
TLR9	Toll-like Receptor 9
TMV	Tobacco Mosaic Virus
ULN	upper limit of normal
US or USA	United States of America
VS	vital signs
WHO	World Health Organization
WOCBP	Women of childbearing potential

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STUDY ADMINISTRATIVE STRUCTURE

Sponsor:	Kentucky BioProcessing, Inc. 3700 Airpark Drive Owensboro, KY 42301 USA Telephone: 270-689-257
Sponsor's Contact:	Oscar (Tony) A. Guzman, MD, CP Clinical Project Lead Kentucky BioProcessing, Inc.
ICON Medical Monitor:	Bart Chapman, MD ICON Clinical Research, LLC 820 West Diamond Avenue, Suite 100 Gaithersburg, MD 20878 USA
ELISA (IgM & IgG) Antibody Titer and Cell Mediated Immunity Laboratories:	VisMederi srl Strada del Petriccio e Belriguardo, 35, 53100 Siena, Italia ICON Central Laboratory 123 Smith Street Farmingdale, NY 11735 USA
Neutralizing Antibody Laboratory:	VisMederi srl Strada del Petriccio e Belriguardo, 35, 53100 Siena, Italia
Clinical Research Organization:	ICON Clinical Research, LLC 820 West Diamond Avenue, Suite 100 Gaithersburg, MD 20878 USA Telephone: 301-944-6800

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President

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Multiple clinical sites may be utilized for Parts A and B. Multiple sites are also planned for Part C.

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2 INTRODUCTION AND BACKGROUND

2.1 Introduction

To date, seven CoVs capable of human infection have been identified, including SARS-CoV, MERS-CoV, and a newly identified CoV (SARS-CoV-2). These 3 viruses, when in the human population, are significant public health risks showing high fatality rates: SARS-CoV = 10%, MERS-CoV = 34.4% and SARS-CoV-2 = 6.1%. The SARS-CoV-2 virus has spread to >180 countries since December 2019, infected >5.7 million humans, and been attributed to >350,000 deaths worldwide [John Hopkins 2020]. These numbers are growing exponentially, creating worldwide health and economic crises. The emergence of this disease and its effects on human health and economic security demands urgent response.

TAP-COVID-19 Vaccine is being developed for the prevention of SARS-CoV-2 infection in healthy adults aged 18 and older. For this Phase 1 Study, the TAP-COVID-19 vaccine will be evaluated with a CpG adjuvant based on preclinical studies showing it provides a Th1 biased immune response against SARS-CoV-2.

2.2 Study Vaccine Background

2.2.1 Receptor Binding Domain Vaccine Strategy

Focusing CoV vaccine efforts around the RBD (S1 domain) of the spike glycoprotein have produced encouraging outcomes. SARS-CoV RBD has been shown to bind the human receptor for ACE-2, contains multiple conformation-dependent epitopes that can elicit high-titer neutralizing antibodies [Wang 2020; Kam 2007; Jaume 2012; Quinlan 2020]. Most relevant to the KBP vaccine strategy, in vivo studies showed that a fusion protein containing RBD-Fc elicited high levels of neutralizing antibodies against SARS-CoV in both immunized rabbits and mice. These antibodies blocked spike interaction with the human receptor ACE-2. Most interestingly, the RBD-Fc protein induced long lasting, potent neutralizing antibody titers maintained for 12 months after immunization – even protecting most vaccinated mice from SARS-CoV challenge [Du 2007; Du 2009]. Importantly, many different versions of SARS or MERS-RBD vaccines have been developed and tested, alone and with adjuvant, produced in mammalian cells, and insect cells and plants. All have shown protection from infection through virus neutralization without accompanying immunopathology associated with full-length or trimerized S protein vaccines [Wang 2020; Kam 2007; Jaume 2012; Quinlan 2020].

2.2.2 TAP-COVID-19 Vaccine – A Novel Vaccine for COVID-19 Disease Prevention

Based on the prior experience with Coronavirus family viruses described above, KBP has developed the RBD-Fc antigen linked to its novel TAP platform to accelerate development of an effective and scalable vaccination strategy. The KBP platform combines the well-established speed and robustness of its transient Nicotiana benthamiana gene expression system with the immune stimulation effects of antigen-association with the inactivated TMV virus structure. Using standardized gene expression and downstream processing strategies, while maintaining a warm

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base of naïve plants, the TAP platform has the potential to rapidly deliver vaccines with significant production potential of millions of doses of vaccine API per month.

Historical preclinical data illustrates the ability of TAP vaccines to provide balanced humoral and cellular responses in mammals allowing efficacious responses to be generated against a wide range of pathogens with different immune correlates of protection [McCormick 2006a; McCormick 2006b; Banik 2015; Arnaboldi 2016; Mallajosyula 2016; Mallajosyula 2014].

The TAP vaccine system offers key advantages of:

- Speed: <10 weeks from sequence to cGMP vaccine
- Balanced immune response: effective stimulation of both Th1 and Th2 arms of the immune system
- Stability: showing room temperature shelf life past 6-months at room temperature with no loss of potency
- Scalability: potential to deliver millions of doses of vaccine API per month
- Robustness: showing safety in murine, ferret, and rabbit preclinical models and efficacy against challenge with seven viruses and three bacterial pathogens, including human influenza virus, Yersinia pestis, Francisella tularensis, and Mycobacterium tuberculosis

2.2.3 CpG Adjuvant

The TAP-COVID-19 Vaccine will be combined with CpG 7909 adjuvant. CpG 7909 is a short (24 nucleotide) synthetic form of DNA that mimics bacterial and viral genetic material that, when included into a vaccine, increases the body's immune response through engagement of TLR9 within antigen presenting dendritic cells and B cells. TLR9-engaging adjuvants are known to generate Th1 cell- and cytokine-mediated immune responses (IFN-γ and IL-2) generated by Th1 cells and IgG2a isotype antibodies and to vaccine antigens and pathogens. Generation of a Th1-biased humoral response may reduce risk associated with antibody-mediated disease enhancement based on FcγRII receptor affinity for Th1 antibodies versus Th2 antibodies [de Alwis 2020; Fierz 2020].

2.2.4 Data Supporting Development of TAP-COVID-19 Vaccine

2.2.4.1 Binding to CR3022 Monoclonal Antibodies

Preliminary data indicates the RBD-Fc intact antigen binds to the human ACE-2 receptor and a SARS-CoV-2 RBD-specific, human neutralizing monoclonal antibody, CR3022. The data shows strong, dose-dependent binding of CR3022 to RBD-Fc antigen and RBD-Fc TAP vaccine. The RBD-Fc candidate antigens show >5X reactivity to CR3022 compared with commercially sourced control SARS spike and RBD reagents. These data suggest that the purified SARS-CoV-2 RBD-Fc antigen maintains essential conformational epitopes in a manner superior to commercially purchased reagents.

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2.2.4.2 Binding to ACE-2 Receptor

Recombinant ACE-2 complexes containing RBD-Fc can be immunoprecipitated by ACE-2 specific antisera in vitro. However, this does not provide a quantitative measure of binding. Quantitative and functional ACE-2 binding was performed using confocal microscopy and analysis by co-localization and competitive binding methods on Vero e6 cells in collaboration with scientists at the University of Louisville, Center for Predictive Medicine and Department of Microbiology & Immunology. The ability of the native agonist, angiotensin II, was compared with the RBD-Fc fusion or concentration dependent ability to block binding of an ACE-2 specific antibody to the receptor on living cells. Influenza H7 hemagglutinin was used as a control. FAM-angiotensin II bound to Vero e6 cells, with an average of a 2.79-fold increase over the non-specific H7 control.

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Binding of the RBD-Fc antigen to Vero e6 cells occurred in a concentration-dependent manner with an increase of 2.58-fold increase over the H7 control. Binding of H7 did not impact detection of ACE-2 by monoclonal antibody at any concentration.

SARS-CoV-2 RBD-Fc fusion antigen shows functional conformation and activity through the binding by CR3022 and ACE-2. Binding to ACE-2 shows similar affinity and specificity as angiotensin II suggesting that the conformation of the spike protein RBD in the antigen-antibody complex is comparable to that observed with native SARS-CoV-2 spike protein. The data suggests that both antigen-antibody complexes display the correct structure necessary to elicit neutralizing antibodies to the RBD of SARS-CoV-2 spike protein.

2.3 Summary of Findings to Date

KBP is also actively developing a quadrivalent seasonal influenza vaccine, TAP-V001, using the TAP platform. Nonclinical studies performed to support TAP-V001 are relevant and supportive of the TAP-COVID-19 program based on the quantities of the vaccine components. In particular, IND-enabling pharmacokinetic/biodistribution and GLP repeat dose toxicology studies have been completed using two different formulations of TAP-V001 vaccine that demonstrated:

- No observed treatment-related or toxicologically significant clinical findings or inoculation site reactogenicity
- No observed treatment-related or toxicologically significant effects for body weights, body weight changes, food consumption, body temperatures, ophthalmology, clinical chemistry, hematology, organ weights, and gross and microscopic pathology
- Dose dependent TMV-specific RT-PCR signal measured at site of injection with rapid clearance from all non-target organs
- Maintenance of TMV-specific RT-PCR signal in immune-processing organs, including lymph nodes and spleen
- Efficacy in two ferret challenge studies, revealing statistically improved H1N1 clearance and statistically equivalent H3N2 clearance compared with Fluzone® control.

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The same platform manufacturing process for production of TAP-V001 is used in the production of TAP-COVID-19, with the exception of the affinity chromatography resin, and a similar drug product formulation is employed.

2.4 Study Rationale

Multiple vaccines have been approved for emergency use for the prevention of SARS-CoV-2, with other vaccines close to being available either through emergency use or licensed vaccines. Although work continues on antiviral treatments for SARS-CoV-2, given the crisis of COVID-19 infections in the world, the fast expansion to the US and other parts of the world, and the global push to vaccinate everyone, additional sources of effective vaccine will be needed.

2.5 Dose Rationale

As SARS-CoV-2 is a newly emergent respiratory viral disease, naïve subjects are expected to require a two dose (prime-boost) immunization regimen to generate a suitable immune response to offer protection from infection. The TAP-COVID-19 vaccine dose levels to be evaluated have been established using a prime-boost dosing strategy in mice as a model species to characterize the vaccine's immunogenicity. Two doses of TAP-COVID-19 have demonstrated a robust and dose-dependent increase in the humoral antibody response to the vaccine in both total antibody and neutralizing antibody titers. This response was seen in separate KBP studies conducted at two different academic centers.

The selected regimen is anticipated to be safe based on nonclinical toxicology studies conducted in rabbits which employed a 4-fold higher antigenic dose levels of a quadrivalent influenza vaccine candidate. There were no toxicologically relevant findings and it was determined that a property of TAP-based vaccines is the trafficking to immune organs (draining lymph nodes and spleen) which may serve as a mechanism for driving the immune response.

Lastly, the proposed rationale for dose level and the dosing regimen is based on historical experience with other pandemic respiratory viral diseases including influenza and prior coronavirus outbreaks and is also consistent with other ongoing SARS-CoV-2 clinical studies.

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3 OBJECTIVES AND ENDPOINTS

3.1 Objectives

3.1.1 Primary Objective

To assess the safety and reactogenicity of two doses of TAP-COVID-19 vaccine with CpG adjuvant for 7 days post vaccination compared with placebo as determined by solicited local and systemic reactogenicity

3.1.2 Secondary Objectives

To compare the frequency of unsolicited AEs of each dose of TAP-COVID-19 vaccine with CpG adjuvant through Day 43 and SAEs, MAAEs, NOCDs, and AESIs through Day 365

Comparisons include:

- High dose (45 µg TAP-COVID-19 vaccine + 0.5 mg CpG) to placebo
- Low dose (15 µg TAP-COVID-19 vaccine + 0.5 mg CpG) to placebo
- High dose (45 µg TAP-COVID-19 vaccine + 0.5 mg CpG) to low dose (15 µg TAP-COVID-19 vaccine + 0.5 mg CpG)

To evaluate the immunogenicity of TAP-COVID-19 vaccine with CpG adjuvant compared with placebo in terms of antibody assessed by GMTs of both spike RBD IgG and IgM antibodies and neutralizing antibody response, GMFR in neutralizing titer from baseline in all treatment groups at Days 8, 22, 29, 43, 90, 181, 273, and 365 relative to baseline

3.1.3 Exploratory Objectives

To assess cellular immunity by measuring the numbers of cytokine producing CD4+ and CD8+ T-cells from PBMCs response to vaccine in all treatment groups at Days 8, 22, 29, 43, 90, 181, 273, and 365 compared to baseline

To assess the immunogenicity of the RBD and Fc component of the vaccine

3.2 Endpoints

3.2.1 Primary Endpoints

Occurrence of Solicited AEs:

- Solicited administration site reactions (eg, pain, tenderness, erythema/redness, induration/swelling) during the 7-day follow-up period after each vaccination (Day 1-8 and Day 22-29)

- Solicited systemic events (eg, fever, nausea/vomiting, diarrhea, headache, fatigue, myalgia) during the 7-day follow-up period after each vaccination (Day 1-8 and Day 22-29)

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3.2.2 Secondary Endpoints

Safety:

- Unsolicited AEs, MAAEs, and AESIs up to Day 43
- SAEs, MAAEs, NOCDs, and AESIs up to Day 365 (approximately 1 year after first vaccination)

Immunogenicity:

- Vaccine ELISA of both RBD IgG and IgM antibodies and neutralizing antibody titers for each treatment group:
  - GMT at baseline and Days 15, 22, 43, 90, 181, 273, and 365
  - GMT ratio ($GMT_{placebo}/GMT_{TAP\text{-}COVID\text{-}19}$) at baseline and Days 22, 29, 43, 90, 181, 273, and 365
  - GMFR at Days 8, 22, 29, 43, 90, 181, 273, and 365 relative to baseline
  - Seroconversion rates on Days 8, 15, 22, 29, 43, 90, 181, 273, and 365. Seroconversion is defined as the proportion of subjects at the respective time point that have detectable antibodies (IgG and IgM) against SARS-CoV-2 Spike Protein RBD following challenge with vaccine (and potentially by natural asymptomatic or symptomatic infection by the virus in case of a placebo subject).
  - GMI on Days 8, 22, 29, 43, 90, 181, 273, and 365

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3.2.3 Exploratory Endpoints

Cellular immunity:

- The number of cytokine producing CD4+ and CD8+ T-cells from PBMCs responsive to vaccine antigens in all treatment groups on Days 8, 22, 29, 43, 90, 181, 273, and 365 compared to baseline

Immunogenicity:

- Anti-RBD and anti-Fc antibodies at baseline and Days 8, 15, 22, 29, 43, 90, 181, 273, and 365

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4 STUDY DESIGN

4.1 Study Design and Overview

This is an FIH, observer-blinded, randomized, placebo-controlled, parallel group study to evaluate the safety and immunogenicity of TAP-COVID-19 vaccine with CpG adjuvant in healthy adult subjects in 2 age groups, Part A (18-49 years) and Part B (50-85 years). A study schematic is presented in Figure 4-1.

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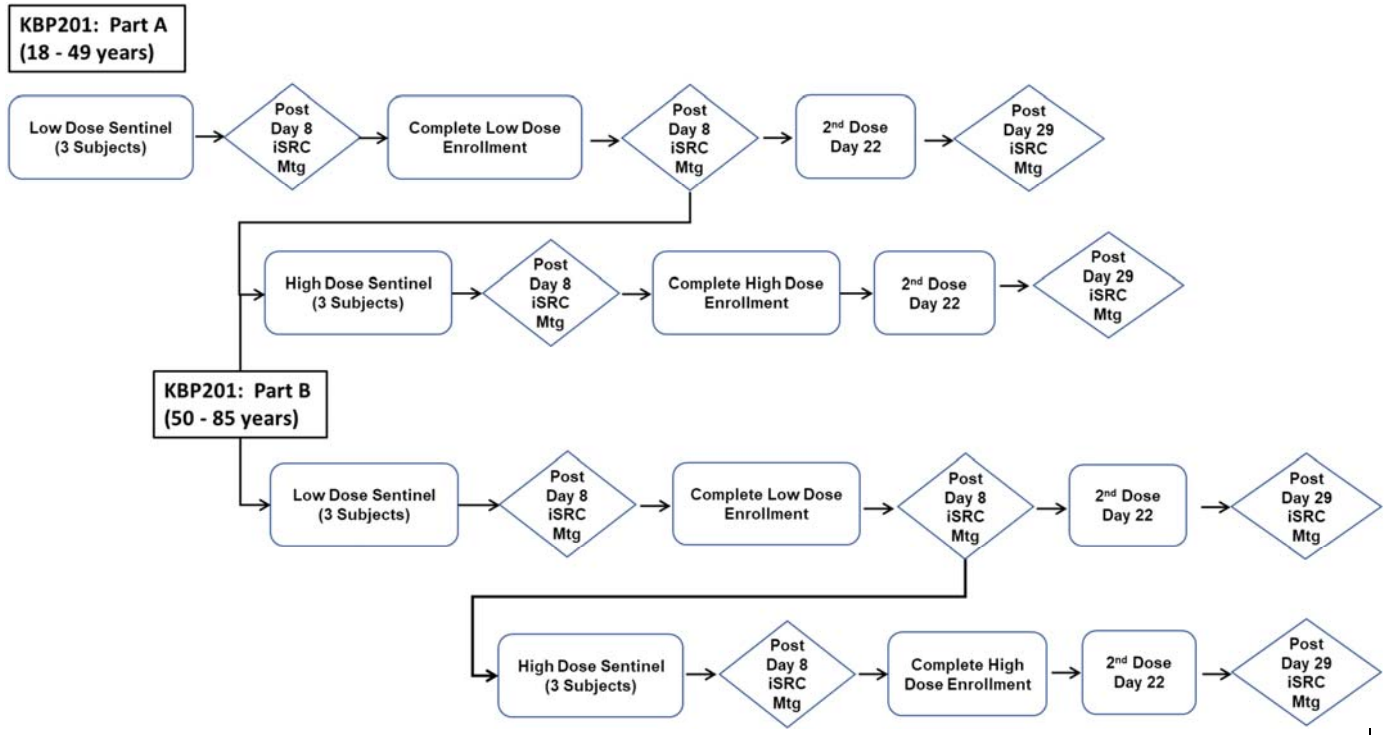
Figure 4-1 Study Schematic for Parts A and B



Abbreviations: High Dose = 45 µg TAP-COVID-19 vaccine + CpG (0.5 mg); iSRC = independent Safety Review Committee;
Low Dose = 15 µg TAP-COVID-19 vaccine+ CpG (0.5 mg); Mtg = meeting

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Part A and Part B:

Subjects will be screened up to 14 days (Day -14 to Day -1) before randomization. Overall, approximately 90 eligible healthy adults ages 18-49 years (inclusive) will be enrolled for Part A and 90 eligible healthy adults ages 50-85 years will be enrolled for Part B.

Sentinel dosing will be utilized in this FIH study. Sentinel cohorts will be used for the following groups:

- Part A (18-49 years) low dose (15 µg TAP-COVID-19 vaccine + 0.5 mg CpG)
- Part B (50-85 years) low dose (15 µg TAP-COVID-19 vaccine + 0.5 mg CpG)
- Part A (18-49 years) high dose (45 µg TAP-COVID-19 vaccine + 0.5 mg CpG)
- Part B (50-85 years) high dose (45 µg TAP-COVID-19 vaccine + 0.5 mg CpG)

Three sentinel subjects from each part will be randomized 2:1 (active:placebo). The iSRC will review the safety data for the sentinel subjects through Day 8 prior to enrollment of the remaining cohort subjects randomized 2:1 (active:placebo). In the event that iSRC has not met for the post Day 8 review because the entire sentinel group (n = 3) has not completed Day 8 before a sentinel subject is to receive the second vaccine on Day 22, the iSRC will meet on an ad hoc basis, to ensure there are no safety concerns and that none of the Individual Discontinuation Criteria (Section 5.5) or Study Halting Rules (Section 5.7.2) have been met, prior to the sentinel subjects receiving the second vaccine.

When all subjects in Part A (18-49 years) low dose have received the first vaccination and have all safety data through Day 8, the iSRC (Section 5.7.1) will convene and review the safety data to ensure that there are no safety concerns and that none of the Study Halting Rules have been met (Section 5.7.2) before recommending that the study enroll Part A high dose and Part B (50-85 years) low dose.

When all subjects in Part B (50-85 years) low dose have received the first vaccination and have all safety data through Day 8, the iSRC will convene and review the safety data to ensure that there are no safety concerns and that none of the Study Halting Rules have been met before recommending that the study enroll Part B high dose.

The iSRC will convene and review the safety data when a minimum of 23 subjects have completed Day 29 after the second vaccination for Part A (low and high dose) and for Part B (low and high dose) to ensure that there are no concerns.

Both Part A (18-49 years) and Part B (50-85 years) will be randomized in a 2:1 ratio (active:placebo) for each treatment dose (15 µg and 45 µg TAP-COVID-19 vaccine + 0.5 mg CpG) for a total of 90 subjects per Part (30 subjects 15 µg TAP-COVID-19 vaccine + 0.5 mg CpG:30 subjects 45 µg TAP-COVID-19 vaccine + 0.5 mg CpG:30 subjects placebo).

Treatment A: TAP-COVID-19 vaccine (15 µg) + CpG (0.5 mg) IM injection on Day 1 and Day 22 (±3 days)

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Treatment B: TAP-COVID-19 vaccine (45 µg) + CpG (0.5 mg) IM injection on Day 1 and Day 22 (±3 days)

Treatment C: Placebo (buffered saline solution) IM injection on Day 1 and Day 22 (±3 days)

Study vaccine will be prepared by an unblinded site pharmacist and administered at the clinical research site on Day 1 and Day 22 (±3 days) by unblinded CRU personnel. Subjects will be observed for immediate AEs and/or reactogenicity for approximately 60 minutes after administration of vaccine. Subjects will be provided with a Diary Card and will be trained to record specifically elicited systemic and local symptoms daily as well as any additional AEs during the 7-day follow-up period after each vaccination. Visits will be conducted at the clinical site on an outpatient basis or as a telephone visit per the Schedule of Assessments and Procedures (Table 1-1). Subjects will participate in the study for approximately 1 year from the first dose.

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AEs and concomitant medications will be captured through Day 43. Blood and serum samples for safety laboratory tests, RBD IgG and IgM antibodies, and neutralizing antibody titers, cell-mediated immunity, and other future biomedical research will be obtained at baseline and before administration of vaccine dose 2 and after each vaccination per the Schedule of Assessments and Procedures (Table 1-1). SAEs, MAAEs, NOCDs, and AESIs only will be captured after Day 43 to study completion (Day 365 [approximately 1 year after vaccination]).

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Prior to receiving a second dose of vaccine, subjects will have the following assessments performed to ensure eligibility: vital signs (including temperature), review of clinical laboratory test results to date, nasopharyngeal swab Day 15 to check for SARS-CoV-2 infection (RT-PCR result must be received by the CRU and negative prior to the second vaccine administration), medical history since last visit including AE assessment for SAEs, Grade 3 AEs, or AESIs that are possibly, probably, or definitely related to study vaccine without a plausible alternative explanation, targeted physical examination, recheck of eligibility criteria, and pregnancy test (as applicable).

Subjects will be monitored for SARS-CoV-2 exposure for potential asymptomatic infection throughout the study.

- If a subject has a positive or borderline ELISA anti-N IgG result, sites should have the subject return for an unscheduled PCR. If the ELISA is positive and the PCR is negative, the sites should follow the subjects using the standard of care under Investigator discretion, retesting ELISA at the next study visit(s) or sooner (per the Investigator's decision).
- If the subject has a positive or borderline ELISA anti-N IgG AND a positive PCR test, the clinical sites should bring the subjects back for repeat PCR testing as described below.
- The clinical sites should continue to collect PCR tests if a subject is experiencing possible COVID-19 symptoms, or had possible exposure to SARS-CoV-2 (ie, close contact tests positive for SARS-CoV-2). Testing will occur every 2 weeks for a total of 4 weeks (if 2 consecutive negative tests) or until negative (x2) after a positive result. Positive results

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will be reported as an AESI (Section 8.2.2) and subjects followed for disease severity, duration, and outcome.

Subjects who are seropositive for SARS-CoV-2 and asymptomatic will be allowed to enroll into Parts A and B of the study as long as the subject is RT-PCR negative.

Additional details for the ELISA test results are presented in Appendix C.

Part C Expansion (Optional):

The Part C Expansion may be conducted to confirm the safety and immunogenicity of a selected dose across the broad target age span using a larger sample size. The proposed sample size was selected based on WHO guidelines on clinical evaluation of vaccines: regulatory expectations Annex I (2001), which states that approximately 300 subjects are needed to identify common local reactogenicity events. A larger sample size will assist in a better characterization of kinetics and range of immunity (neutralizing antibody titers) and provide a more reliable output of seropositivity and seroconversion to TAP-COVID-19 immunization. With the limited clinical experience with SARS-CoV-2 vaccines and the current lack of a biomarker correlate of protection, the generation of this larger data set is relevant to inform the design and implementation of a Phase 3 program. After review of safety and immunogenicity data from Parts A and B through Day 43, a dose for the Phase II expansion study will be recommended by the iSRC. Progression to Part C will only take place after CBER has had the opportunity to review the human clinical plus additional nonclinical data and concurs with the plan to proceed with enrollment. Subjects ≥18 years of age will be enrolled and randomized 1:1 (selected active dose:placebo). Up to 1000 subjects will be enrolled at the chosen dose to provide expanded dose confirmation, safety, and immunogenicity data. Although all subjects in Part C will have safety laboratory tests performed at screening, only the first 200 subjects in Part C will have safety laboratory tests performed at all post-dose time points. The remaining subjects in Part C will not have safety laboratory tests performed at any of the post-dose time points unless the Investigator deems it necessary.

Subjects who are seropositive for SARS-CoV-2 and asymptomatic will be allowed to enroll into Part C of the study.

4.1.1 Duration of Study

Each subject will receive two doses of study vaccine or placebo, the first on Day 1 and the second on Day 22 (±3 days). The total duration of subject participation is approximately 1 year (including screening, treatment, and follow-up periods).

4.1.2 Interim Safety Data Review

For all of the sentinel groups, the iSRC will meet to review the sentinel subjects' safety and tolerability data through Day 8. In the event that iSRC has not met for the post Day 8 review because the entire sentinel group (n = 3) has not completed Day 8 before a sentinel subject is to receive the second vaccine on Day 22, the iSRC will meet on an ad hoc basis, to ensure there are no safety concerns and that none of the Individual Discontinuation Criteria (Section 5.5) or Study

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Halting Rules (Section 5.7.2) have been met, prior to the sentinel subjects receiving the second vaccine.

When all subjects in Part A (18-49 years) low dose have received the first vaccination and have all safety data through Day 8, the iSRC (Section 5.7.1) will convene and review the safety data to ensure that there are no safety concerns and that none of the Study Halting Rules have been met (Section 5.7.2) before recommending that the study enroll Part A high dose and Part B low dose. The same strategy will be used for Part B when going from low to high dose.

The iSRC will be asked to review unblinded immunogenicity and safety data when the first 30 subjects vaccinated in the Part A low dose group (including active and placebo subjects) have data available from Day 1 through Day 43 for an assessment of the risk-benefit of the trial. For the interim analysis, treatment codes will be unblinded and only after the data are deemed ready for the analysis and the data has been monitored. The unblinded review will be completed by the iSRC only and the other team members (CRO [except for the unblinded team members preparing the data for unblinded iSRC review], Investigator, and site personnel) will remain blinded until completion of the study. The Sponsor will be unblinded at the interim analysis.

The iSRC will also meet when a minimum of 23 subjects have completed Day 29 after the second vaccination for Part A (low and high dose) and for Part B (low and high dose) to review safety data to ensure that there are no concerns.

The iSRC will also review all data through Day 43 for Part A and for Part B in both dose groups to monitor for ongoing safety concerns and immunogenicity analysis. When the Parts A and B Day 43 (low and high dose) review is complete, the iSRC will recommend a dose for the Part C Expansion (optional). Progression to Part C will only take place after CBER has had the opportunity to review the Day 43 data from Parts A and B and concurs with the plan to proceed with enrollment.

4.1.3 Definition of Study Completion

End-of-study procedures will be performed as specified in the Schedule of Assessments and Procedures (Table 1-1); subjects who withdraw from the study early will have EOS procedures performed at the time of discontinuation. If a subject refuses to return for the EOS blood samples, the safety follow-up will be completed via telephone. Subjects with ongoing clinically significant clinical or laboratory findings will be followed until the finding is resolved or medically stable; reasonable attempts will be made to follow-up with subjects. The subject's participation in the study will end once all study assessments and follow-up have been completed.

4.1.4 End of Study

The end of the study is defined as the date when the last subject has completed all study procedures up to and including the EOS/early termination visit as specified in the Schedule of Assessments and Procedures (Table 1-1).

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5 SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Inclusion Criteria

Subjects must meet all inclusion criteria to be eligible for study participation. In addition, racial and ethnic minorities will be sought to obtain a diverse study population.

All Subjects

1. Subject read, understood, and signed the ICF.
2. Healthy adult males and females 18-49 years of age (Part A) or 50-85 years of age (Part B), inclusive, at screening.
3. RT-PCR negative at time of screening.
4. BMI of ≥ 18 and ≤ 30 kg/m^2 (National Heart, Lung, and Blood Institute) at screening. BMI = weight (kg)/(height [m])^2.
5. Must be in general good health before study participation with no clinically relevant abnormalities that could interfere with study assessments.
6. WOCBP and men whose sexual partners are WOCBP must be able and willing to use at least 1 highly effective method of contraception (ie, include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy, hormonal oral [in combination with male condoms with spermicide], transdermal, implant, or injection, barrier [ie, condom, diaphragm with spermicide]; intrauterine device; vasectomized partner [6 months minimum], clinically sterile partner; or abstinence) during the study.
   - A female subject is considered to be a WOCBP after menarche and until she is in a postmenopausal state for 12 consecutive months (without an alternative medical cause) or otherwise permanently sterile.
   - Note: Subjects not of childbearing potential are not required to use any other forms of contraception during the study. Non-childbearing potential is defined as subject confirmed:
     - Surgical sterilization (eg, bilateral oophorectomy, bilateral salpingectomy, bilateral occlusion by cautery [Essure System is not acceptable], hysterectomy, or tubal ligation)
     - Postmenopausal (defined as permanent cessation of menstruation for at least 12 consecutive months prior to screening) with FSH ≥ 30 mIU/mL at screening
7. WOCBP must have a negative urine pregnancy test before each vaccination.
8. Must be able to attend all visits, including unscheduled visits if respiratory symptoms suggestive of SARS-CoV-2 infection develop during the study, for the duration of the study and comply with all study procedures, including daily completion of the Diary Card for 7 days after each injection.

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5.2 Exclusion Criteria

Subjects will not be eligible for study participation if they meet any of the exclusion criteria, or will be discontinued at the discretion of the Investigator if they develop any of the exclusion criteria during the study.

Parts A and B

1. History of an acute or chronic medical condition including dementia that, in the opinion of the Investigator, would render vaccination unsafe or would interfere with the evaluation of responses. Chronic conditions that are NOT included on the CDC's list of subjects at higher risk for severe illness from SARS-CoV-2 (CDC COVID-19 website) are acceptable if the condition has been stable for the 3 months prior to vaccine administration (Day 1), with no medication changes, and no hospitalization in the past 6 months.
2. History of any medical conditions that place subjects at higher risk for severe illness due to SARS-CoV-2 including but not limited to cancer, chronic kidney disease at any stage, chronic lung disease, dementia or other neurological conditions, diabetes (Type 1 or Type 2), Down syndrome, heart conditions, HIV infection, immunocompromised state (weakened immune system), liver disease, overweight/obesity, pregnancy, sickle cell disease or thalassemia, smoker (current or former), transplants (solid organ or blood stem cell), stroke or cerebrovascular disease, and substance use disorders. (See the latest updates at the CDC COVID-19 website.)
3. History of ongoing clinical condition or medication or treatments that may adversely affect the immune system.
4. Individuals who are RT-PCR positive for SARS-CoV-2 at screening or prior to second dose of TAP-COVID-19 vaccine.
5. Individuals who are at increased risk of exposure to SARS-CoV-2 (eg, healthcare workers, emergency responders).
6. Close contact of anyone known to have SARS-CoV-2 infection within 30 days prior to vaccine administration.
7. Living in a group care facility (eg, assisted living or nursing home).
8. Individuals with any elevated (Grade 1 or higher) laboratory test assessed as clinically significant for age by the Investigator at screening (Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007), Tables for Laboratory Abnormalities).
9. Individuals with elevated (Grade 1 or higher) liver function enzyme at screening, may repeat testing once to re-assess clinical significance. If the retest comes back within normal range, the subject will be eligible for enrollment with Investigator and Medical Monitor approval. See below for the criteria for excluding subjects with elevated liver enzymes (once confirmed by retest):
    - ALP, ALT, AST, or GGT >1.5 × ULN
    - Total bilirubin >1.6 × ULN

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10. Active neoplastic disease (excluding nonmelanoma skin cancer that was successfully treated) or a history of any hematological malignancy. "Active" is defined as having received treatment within the past 5 years.
11. Long-term (greater than 2 weeks) use of oral or parenteral steroids, high-dose inhaled steroids (>800 µg/day of beclomethasone dipropionate or equivalent), or immunomodulatory drugs within 6 months before screening (nasal and topical steroids are allowed).
12. History of autoimmune, inflammatory disease, or potential immune-mediated medical conditions (Appendix B).
13. Women currently pregnant, lactating, or planning a pregnancy between enrollment and 181 days after randomization.
14. History of Guillain-Barré Syndrome.
15. History of anaphylactic-type reaction to injected vaccines.
16. Known or suspected hypersensitivity to 1 or more of the components of the vaccine, including thimerosal, tobacco, and CpG adjuvant.
17. History of alcohol abuse, illicit drug use, physical dependence to any opioid, or any history of drug abuse or addiction within 12 months of screening.

    Note: In those regions where cannabis use is legal, it will be left to the discretion of the Investigator to decide if a subject is an occasional user or an abuser of cannabis. The Investigator should discuss user/abuser status on a case-by-case basis with the Medical Monitor prior to enrollment.
18. Acute illness or fever within 3 days before study enrollment (enrollment may be delayed for full recovery if acceptable to the Investigator).
19. Individuals currently participating or planning to participate in a study that involves an experimental agent (vaccine, drug, biologic, device, or medication); or who have received an experimental agent within 1 month (3 months for immunoglobulins) before enrollment in this study; or who expect to receive another experimental agent during participation in this study.
20. Receipt of immunoglobulin or another blood product within the 3 months before enrollment in this study or those who expect to receive immunoglobulin or another blood product during this study.
21. Individuals who intend to donate blood within 6 months after the first vaccination.
22. Individuals using prescription medications for prophylaxis of SARS-CoV-2.
23. Individuals who plan to receive another vaccine within the first 3 months of the study except influenza vaccine which should not be given within 2 weeks of study vaccine.
24. Receipt of any other approved SARS-CoV-2 vaccine prior to the first study vaccine or within 90 days after administration of the first study vaccine.
25. Receipt of any other experimental coronavirus vaccine at any time prior to or during the study.
26. Receipt of any investigational vaccine or drug within 1 month of enrollment and through the end of the study (1 year after first vaccination).

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27. Plan to travel outside the subjects' country of residence from enrollment through Day 43.
28. History of surgery or major trauma within 12 weeks of screening, or surgery planned during the study.
29. Significant blood loss (>450 mL) or has donated 1 or more units of blood or plasma within 6 weeks prior to study participation.
30. Strenuous activity (as assessed by the Investigator) within 48 hours prior to dosing (Days 1 and 22).
31. A positive urine drug screen without evidence of corresponding prescribed concomitant medication(s) at Screening. Note: A positive drug screen result with a corresponding prescribed concomitant medication will be allowed if, in the opinion of the investigator and Medical Monitor, the concomitant medication does not make the subject unsuitable to participate in the clinical trial. For a positive tetrahydrocannabinol result, refer to Exclusion Criteria #17.
32. Positive alcohol screen.
33. Positive screen for HIV-1 and HIV-2 antibodies, HBsAg, or HCV antibody.
34. Involved in the planning or conduct of this study.
35. Unwilling or unlikely to comply with the requirements of the study.
36. Subject is an employee, contractor, friend of or relative of any employee of Sponsor, CRO, study site or site affiliate.

Part C

If the study proceeds to the Part C Expansion study to confirm the safety and immunogenicity of the selected dose of vaccine, the following exclusion criteria (Number, from Parts A and B above) will be not applicable.

(5) Individuals who are at increased risk of exposure to SARS-CoV-2 (eg, healthcare workers, emergency responders).

(6) Close contact of anyone known to have SARS-CoV-2 infection within 30 days prior to vaccine administration.

(7) Living in a group care facility (eg, assisted living or nursing home).

(31) A positive urine drug screen without evidence of corresponding prescribed concomitant medication(s) at Screening. Note: A positive drug screen result with a corresponding prescribed concomitant medication will be allowed if, in the opinion of the investigator and Medical Monitor, the concomitant medication does not make the subject unsuitable to participate in the clinical trial.

(32) Positive alcohol screen.

(33) Positive screen for HIV-1 and HIV-2 antibodies, HBsAg, or HCV antibody (Parts A and B). For Part C, subjects known to be HIV positive or have active Hepatitis B or C infection will be excluded.

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5.3 Screen Failures

Subjects who are discontinued from the study prior to study vaccine administration will be considered screen failures and may be re-screened as long as the subject was not discontinued from the study due to noncompliance with the protocol (eg, positive urine drugs of abuse screen, etc.). If the subject is re-screened, the subject must be re-consented and have all of the screening procedures re-performed.

Screen failure data will not be recorded in the eCRF.

5.4 Decision to Administer Second Vaccination

Prior to administering the second vaccination, subjects will have the following procedures/assessments performed:

- Inclusion/exclusion criteria recheck (including absence of acute illness or new medical condition)
- Oral temperature
- Targeted physical examination
- Vital signs
- Review of clinical safety laboratory test results to date
- Urine pregnancy test, as applicable
- Nasopharyngeal swab on Day 15 to check for SARS-CoV-2 infection (result must be received by the CRU and negative prior to the second vaccine administration).
- Medical history since last visit including AE assessment for SAEs, Grade 3 AEs or AESIs that are possibly, probably, or definitely related to study vaccine without a plausible alternative explanation
- Check of Study Halting Rules (Section 5.7.2)

All assessments must be normal or be in agreement with inclusion/exclusion criteria in order for a subject to receive the second vaccination dose.

For all of the sentinel groups, the iSRC will meet to review the sentinel subjects' safety and tolerability data through Day 8. In the event that iSRC has not met for the post Day 8 review because the entire sentinel group (n = 3) has not completed Day 8 before a sentinel subject is to receive the second vaccine on Day 22, the iSRC will meet on an ad hoc basis, to ensure there are no safety concerns and that none of the Individual Discontinuation Criteria (Section 5.5) or Study Halting Rules (Section 5.7.2) have been met, prior to the sentinel subjects receiving the second vaccine.

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5.5 Individual Discontinuation Criteria

The occurrence of the following findings in an individual subject may result in discontinuation from the study vaccine. Subjects will be asked to participate in the scheduled Follow-up Visits, including at a minimum Day 365, to check safety and immunogenicity.

- Subjects experiences an SAE assessed as possibly related, probably related, or related to study vaccine without a plausible alternative explanation.
- Subject has generalized urticaria during the 7-day post vaccination period.
- Subject develops a Grade 4 local reaction for which there is no alternative plausible explanation.
- Subject experiences laryngospasm, bronchospasm, or anaphylaxis after vaccine administration considered related to the vaccine.
- Subject develops a fever >40°C/104°F during the 7 days post vaccination period that is assessed as possibly related, probably related, or related to study vaccine without a plausible alternative explanation.
- Single Grade 3 AEs or AESIs that are possibly, probably, or definitely related to study vaccine without a plausible alternative explanation.
- Subject experiences any Grade 3 or higher abnormality in the same laboratory parameter determined by the Investigator or medical monitor as clinically significant and that are assessed as possibly related, probably related, or related to study vaccine without a plausible alternative explanation.

5.6 Subject Withdrawal

Subjects are free to withdraw from the study at any time, for any reason, and without prejudice to further treatment. The Investigator may withdraw a subject if, in the Investigator's judgment, continued participation would pose unacceptable risk to the subject or to the integrity of the study data. All procedures for early withdrawal must be completed. Reasons for withdrawal may include:

- AE
- SAE that is possibly related, probably related, or related, without a plausible alternative explanation
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Study terminated by Sponsor
- Withdrawal by subject
- Death
- Other

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Subjects who are withdrawn for reasons other than AEs may be replaced.

In the event of a subject's withdrawal from study vaccine, the Investigator will promptly notify the Sponsor and will make every effort to complete the EOS assessments, unless the subject withdraws consent. All withdrawn subjects with ongoing clinically significant clinical or laboratory findings will be followed until the finding is resolved or medically stable; reasonable attempts will be made to follow-up with subjects. The subject will also be asked to participate in a Follow-up Visit at approximately Day 365 to check safety and immunogenicity.

Subjects may be withdrawn from receiving the second dose of the study vaccine if they meet specific Study Halting Rules (see Section 5.7.2) or Individual Discontinuation Criteria (Section 5.5). If a subject is withdrawn due to meeting a Study Halting Rule or Individual Discontinuation Criteria, they will be asked to participate in the scheduled Follow-up Visits, including at a minimum Day 365, to check safety and immunogenicity.

5.7 Independent Safety Review Committee, Study Stopping Rules, and Study Termination

5.7.1 Independent Safety Review Committee

A safety review will be performed by the iSRC according to details established at the start of the study and provided in the iSRC charter. The Investigator will provide a brief summary to the iSRC of any pertinent safety events prior to the iSRC meeting. The three member iSRC will consist of, at a minimum, two physicians with experience in vaccines and one statistician.

The iSRC will review the safety and tolerability data through Day 8 for each of the sentinel subject groups prior to the enrollment of the remaining cohort subjects. In the event that iSRC has not met for the post Day 8 review because the entire sentinel group (n = 3) has not completed Day 8 before a sentinel subject is to receive the second vaccine on Day 22, the iSRC will meet on an ad hoc basis, to ensure there are no safety concerns and that none of the Individual Discontinuation Criteria (Section 5.5) or Study Halting Rules (Section 5.7.2) have been met, prior to the sentinel subjects receiving the second vaccine.

The iSRC will be convened to review all available safety data including solicited AEs, unsolicited AEs, SAEs, MAAEs, NOCDs, AESIs, vitals, safety laboratory, and physical exams results of Part A low dose when all subjects have received the first vaccination and have all safety data through Day 8. If there are no safety concerns after the iSRC meeting, study enrollment will continue to Part A high dose and Part B low dose. The same strategy will be used to move from Part B low dose to Part B high dose.

The iSRC will also meet when a minimum of 23 subjects have completed Day 29 after the second vaccination for Part A (high and low dose) and for Part B (high and low dose) to review safety data to ensure that there are no concerns.

The iSRC will be asked to review unblinded immunogenicity and safety data when the first 30 subjects vaccinated in the Part A low dose group (including active and placebo subjects) have data available from Day 1 through Day 43 for an assessment of the risk-benefit of the trial. For the

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interim analysis, treatment codes will only be unblinded by treatment group (not by individual subjects) and only after the data are deemed ready for the analysis and the data has been monitored. The unblinded review will be completed by the iSRC only and the other team members (CRO [except for the unblinded team members preparing the data for unblinded iSRC review], Investigator, and site personnel) will remain blinded. The Sponsor will be unblinded at the interim analysis (Day 43). The iSRC/Sponsor will communicate immunogenicity data to the study team in a blinded manner so that clinical development decisions for additional studies can be made by the Sponsor.

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Cohort dose continuation/escalation will only occur if the iSRC determines that the current dose was safe and well tolerated. If justified by cumulative safety and tolerability data, the iSRC can dose escalate per protocol, select an intermediate dose (lower or higher), or repeat a dose. The decision to allow dose continuation/escalation into the next cohort will be documented and this decision, along with the safety information, will be communicated to the site.

The iSRC will also meet on an ad hoc basis if any of the Study Halting Rules are met (Section 5.7.2). If a Study Halting Rule is met, the iSRC will proceed with an unblinded review of available safety data. After the meeting, the iSRC will make 1 or more of the following recommendations:

- All vaccinations should resume
- Specific treatment groups should be discontinued while other treatment groups should resume vaccinations
- No vaccinations should resume
- Modifications to study conduct (eg, additional safety or laboratory assessments)

The blinded medical monitor will also assess cumulative safety information for this study per the Medical Monitoring Plan and advise the Sponsor of any of the safety findings (Section 5.7.2) have occurred.

The iSRC will review unblinded safety data for any subject who dies, requires ICU admission due to SARS-CoV-2 infection, develops an AESI (Section 8.2.2) of autoimmune disease or potential immune-medicated medical condition (Appendix B), or experiences vaccine-associated enhanced respiratory disease. If the subject had received TAP-COVID-19, the iSRC may decide whether a study halt for vaccine-enhanced disease is required based on a review of all available clinical and preclinical safety and immunogenicity data.

5.7.2 Study Halting Rules

The occurrence and confirmation of 1 or more of the following findings will result in suspension of further enrollment and study vaccine administration pending urgent review (within 1 week) of the safety data by the iSRC. Subjects who are withdrawn from study vaccine (if applicable) will continue to be monitored (Section 5.6) for safety and immunogenicity.

1. One or more subjects experience an SAE assessed as possibly related, probably related, or related to study vaccine without a plausible alternative explanation.

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2. One or more subjects have generalized urticaria during the 7-day post vaccination period.
3. One or more subjects develop a Grade 4 local reaction for which there is no alternative plausible explanation.
4. One or more subjects experiences laryngospasm, bronchospasm, or anaphylaxis after vaccine administration considered related to the vaccine.
5. One or more subjects develop a fever >40°C/104°F during the 7 days post vaccination period that is assessed as possibly related, probably related, or related to study vaccine without a plausible alternative explanation.
6. Two or more subjects within an individual treatment group, or 2 or more subjects across treatment groups, experience any Grade 3 or higher abnormality in the same laboratory parameter determined by the Investigator or medical monitor as clinically significant and that are assessed as possibly related, probably related, or related to study vaccine without a plausible alternative explanation.

   Note: An unblinded statistician or designee will assist with determining whether stopping rule #6 is met.
7. Two or more subjects across treatment groups experience a Grade 3 or higher AE, MAAE, or AESI of the same or similar preferred terms (as categorized by MedDRA) assessed as possibly related, probably related, or related to study vaccine without a plausible alternative explanation.
8. Any subject with severe SARS-CoV-2 infection will be assessed for the possibility of vaccine-associated enhanced respiratory disease. Severe SARS-CoV-2 infection is defined as individuals who have virologically confirmed SARS-CoV-2 infection with any of the following:
   - Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 breaths per minute, heart rate ≥ 125 bpm, $SpO_2 \leq 93\%$ on room air at sea level or PaO_2/FiO_2 < 300 mmHg)
   - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or ECMO)
   - Evidence of shock (systolic blood pressure < 90 mmHg, diastolic blood pressure < 60 mmHg, or requiring vasopressors)
   - Significant acute renal, hepatic, or neurologic dysfunction
   - Admission to an ICU
   - Death due to SARS-CoV-2 infection

5.7.3 Study Termination

The study may be terminated at any time by the Sponsor if serious side effects occur, if potential risks to study participants are identified, if the Investigator does not adhere to the protocol, or if, in the Sponsor's judgment, there are no further benefits to be achieved from the study. In the event

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that the clinical development of the study vaccine is discontinued, the Sponsor shall inform all Investigators/institutions and regulatory authorities.

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6 TREATMENT OF SUBJECTS

6.1 Identity of Study Vaccines

The TAP-COVID-19 vaccine is comprised of a purified recombinant SARS-CoV-2 RBD-Fc conjugated to a TMV NtK carrier. The TAP-COVID-19 vaccine will be combined with CpG 7909 adjuvant prior to administration.

The product will be formulated and shipped as multi-dose vials. The vaccine doses will be diluted as appropriate by the site pharmacist to 15 µg or 45 µg doses of antigen along with 0.5 mg CpG adjuvant to be delivered in a single 0.5 mL IM injection. A detailed description for vaccine preparation is provided in the pharmacy manual.

Buffered saline solution (with thimerosal) will be used as placebo.

A description of the study vaccines is presented in Table 6-1.

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Table 6-1 Study Vaccines

Study Vaccine	Dosage Form (Volume, Route)	TAP-COVID-19 Dose	Manufacturer
TAP-COVID-19 + CpG (0.5 mg)	Injectable solution, (0.5 mL, intramuscular injection)	15 µg	Kentucky BioProcessing, Inc.
TAP-COVID-19 + CpG (0.5 mg)	Injectable solution, (0.5 mL, intramuscular injection)	45 µg	Kentucky BioProcessing, Inc.
Placebo (buffered saline solution)	Injectable solution, (0.5 mL, intramuscular injection)	Not applicable	Kentucky BioProcessing, Inc.

TAP-COVID-19, CpG adjuvant, and the placebo (buffered saline solution) will be sourced by KBP.

6.2 Treatments Administered

Both Part A (18-49 years) and Part B (50-85 years) will be randomized in a 2:1 ratio (active:placebo) for each treatment dose (15 µg and 45 µg TAP-COVID-19 vaccine + 0.5 mg CpG) for a total of 90 subjects per Part (30 subjects 15 µg TAP-COVID-19 vaccine + 0.5 mg CpG:30 subjects 45 µg TAP-COVID-19 vaccine + 0.5 mg CpG:30 subjects placebo).

Treatment A: TAP-COVID-19 vaccine (15 µg) + CpG (0.5 mg) IM injection on Day 1 and Day 22 (±3 days)

Treatment B: TAP-COVID-19 vaccine (45 µg) + CpG (0.5 mg) IM injection on Day 1 and Day 22 (±3 days)

Treatment C: Placebo (buffered saline solution) IM injection on Day 1 and Day 22 (±3 days)

The IM dose for Part C Expansion (optional) will be determined after reviewing the safety and immunogenicity data through Day 43 from Parts A and B (low and high dose).

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6.3 Method of Assigning Subjects to Treatment Groups

ICON will prepare the randomization scheme in accordance with its SOPs and the randomization plan, which reflect GCP standards. Refer to Section 9.3 for a description of randomization methods. Eligible subjects will be assigned to a treatment group according to the list of subject randomization assignments.

6.4 Measurements of Treatment Compliance

All study vaccine doses will be prepared and administered by delegated and trained staff at the clinical site(s). Details regarding dosing, including the dose administered and the date and time of dosing, will be recorded.

6.5 Study Vaccine Storage, Accountability, and Retention

6.5.1 Storage Conditions

The Investigator will ensure that all the study vaccines are stored per the instructions accompanying the study vaccine. In addition, the Investigator will ensure that study vaccines are handled in accordance with the FDA regulations concerning the storage and administration of investigational products.

Refer to the SRM for additional study vaccine storage instructions.

6.5.2 Drug Accountability and Retention

The Investigator must ensure that all study vaccine supplies are kept in a secure locked area with access limited to those authorized by the Investigator. The Investigator must maintain accurate records of the receipt of all study vaccine shipped by KBP or their representative, including but not limited to the date received, lot number, expiration date, amount received, and the disposition of all study vaccine. Current dispensing records will also be maintained including the date and amount of study vaccine dispensed and the subject receiving the drug. All remaining study vaccine not required by regulations to be held by the clinical site(s) must be returned to KBP or their representative immediately after the study is completed.

6.6 Packaging and Labeling

6.6.1 Study Vaccine

Study vaccine will be supplied as a concentrated injectable solution packaged in 10-mL multi-dose vials with preservative (thimerosal). CpG sterile solution will be supplied as a concentrated solution with preservative (thimerosal). Placebo will be buffered saline solution with preservative (thimerosal) provided by KBP.

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6.6.2 Blinding of Treatment Assignment

ICON will maintain the randomization code in a secure location with controls to prevent unauthorized access, including the computer program written to generate the randomization, randomization codes, program log, seed number used by the program, copy of the randomization plan along with approval documentation as appropriate, and the write-protected electronic storage medium.

The site and CRO will name an unblinded statistician to provide the randomization code. The pharmacists will be unblinded. Since the placebo and vaccine will not be identical in appearance, the staff member administering the doses will be unblinded and will not participate in any additional study activities. In order to preserve the blind, study vaccine will be prepared and administered in a manner that masks the content for both the subject and any observers. Investigators, site staff, subjects, CRO [except for the unblinded team members preparing the data for unblinded iSRC review] will remain blinded until the completion of the study. The Sponsor will remain blinded to individual subjects' treatment assignment from the beginning of the study through Day 43. When the data is unblinded for the interim analysis after all subjects complete Day 43, the Sponsor will be unblinded

6.6.3 Unblinding of Treatment Assignment

6.6.3.1 Unblinding for Adverse Event/Safety Reasons

Should an SAE or other circumstance require that the blind be broken to ensure subject safety, the Investigator must immediately notify the medical monitor and/or Sponsor. ICON/designee will notify the Sponsor as soon as possible and will release the treatment assignment of the subject to the appropriate personnel in accordance with the applicable SSP.

If the treatment assignment is unblinded by the site pharmacist or any party other than ICON, the Investigator must notify ICON in writing and document the course of events in the source records. Any subject for whom the treatment code is prematurely released will be withdrawn from the study.

6.6.3.2 Unblinding for Interim Analyses

An unblinded interim analysis will be performed on the safety and immunogenicity data collected for each of the 4 dose groups (Part A low dose, Part A high dose, Part B low dose, and Part B high dose). Unblinded interim analysis will occur for the Part A low dose group (including active and placebo subjects) when the first 30 subjects vaccinated have data available from Day 1 through Day 43. The remaining cohorts will have an unblinded interim analysis performed when all subjects in the cohort have data from Day 1 through Day 43. For the interim analysis, treatment codes will be unblinded after the data are deemed ready for the analysis and the data has been monitored. The CRO [except for the unblinded team members preparing the data for unblinded iSRC review], Investigator, and clinical staff will not have access to the unblinded treatment group interim analyses and will remain blinded until completion of the study. The Sponsor will be unblinded at the interim analysis. The iSRC will communicate immunogenicity data to the study

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team in a blinded manner so that clinical development decisions for additional studies can be made by the Sponsor.

6.7 Concomitant Medications and Procedures and Other Restrictions

6.7.1 Concomitant Medications and Procedures

Any medication taken by a subject from 30 days prior to the screening visit through the first 43 days of the study and the reason for its use will be documented.

Previous prescription medication for mild chronic health disorders (eg, hypertension or hypercholesterolemia) or maintenance (eg, contraception) will be allowed at the discretion of the Investigator as long as the subject has been on a stable dose for at least 3 months. Subjects should continue their regular maintenance medications throughout study participation unless instructed to discontinue or change by the Investigator or their personal physician. If concomitant medications are discontinued by a subject during study conduct the subject should notify the Investigator. Subjects should refrain from starting new medications, modifying current concomitant medications, or receiving vaccinations during study participation unless prescribed by the Investigator for treatment of specific clinical events.

Subjects should not receive any vaccine within 1 month before screening.

Subjects should not be using prescription medications for the prophylaxis of SARS-CoV-2.

Subjects should not participate or plan to participate in a study that involves an experimental agent (vaccine, drug, biologic, device, or medication); or should not have received an experimental agent within 1 month before enrollment in this study; or who expect to receive another experimental agent during participation in this study.

A positive drug screen result with a corresponding prescribed concomitant medication will be allowed if, in the opinion of the investigator and Medical Monitor, the concomitant medication does not make the subject unsuitable to participate in the clinical trial.

6.7.2 Other Restrictions

Subjects will be instructed to adhere to the following restrictions:

- Strenuous activity (as assessed by the Investigator) is prohibited from 48 hours prior to the days safety laboratory blood will be collected
- Subjects are not permitted to consume alcohol for 3 days prior to vaccination and should refrain from consumption of alcohol until 7 days post vaccination.
- Subjects should refrain from blood donation for 6 months post vaccination.
- Subjects should not participate or plan to participate in a study that involves an experimental agent (vaccine, drug, biologic, device, or medication); or should not have received an experimental agent within 1 month before enrollment in this study; or who expect to receive another experimental agent during participation in this study.

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7 STUDY ASSESSMENTS AND PROCEDURES

Subjects will undergo study procedures and assessments at time points specified in the Schedule of Assessments and Procedures (Table 1-1).

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7.1 Pandemic Safety Procedures

Appropriate measures will be taken to ensure the safety of both study staff and study subjects including social distancing and appropriate personal protective equipment.

7.2 Medical and Surgical History

The Investigator or designee will collect a complete medical and surgical history at screening. Medical and surgical history will be collected at CRU visits to determine if any changes have occurred since screening.

7.3 Demographic Characteristics

Demographic characteristics including sex, age, race, and ethnicity will be recorded. Tobacco use and history will also be documented.

7.4 Physical Measurements

Height (cm) and body weight (kg) without shoes will be recorded. BMI will be calculated using the height obtained at screening.

7.5 Immunogenicity

Blood samples for antibody titers will be collected per Table 1-1 to assess:

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- Vaccine (ELISA for IgM and IgG, total antibody) and neutralizing antibody titers (virus microneutralization) for each treatment group:
  - GMT ratio ($GMT_{placebo}/GMT_{TAP\text{-}COVID\text{-}19}$)
  - Seroconversion rate is defined as the proportion of subjects at the respective time point that have detectable antibodies (IgG and IgM) against SARS-CoV-2 Spike Protein RBD following challenge with vaccine (and potentially by natural asymptomatic or symptomatic infection by the virus in case of a placebo subject).
- Anti-RBD and anti-Fc antibodies

Blood samples for cellular immunity (PBMCs) will be collected per Table 1-1. The numbers of cytokine producing CD4+ and CD8+ T-cells from PBMCs responsive to vaccine antigens will be analyzed using a validated procedure.

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PBMC and serum samples for future research will also be collected (5-7 aliquots [1 mL]) at the time points outlined in Table 1-1.

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Immunogenicity sample collection, processing, and shipping details will be outlined in a separate SRM.

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7.6 SARS-CoV-2 Exposure and Asymptomatic Monitoring

Subjects will be monitored for SARS-CoV-2 exposure for potential asymptomatic infection throughout the study. CRU staff will interview subjects about any potential exposure to the virus. If a subject has had potential exposure, the CRU will perform an unscheduled nasopharyngeal swab. Subjects will not be discontinued from the study due to positive SARS-CoV-2 test results.

- If a subject has a positive or borderline ELISA anti-N IgG result, sites should have the subject return for an unscheduled PCR. If the ELISA is positive and the PCR is negative, the sites should follow the subjects using the standard of care under Investigator discretion, retesting ELISA at the next study visit(s) or sooner (per the Investigator's decision).
- If the subject has a positive or borderline ELISA anti-N IgG AND a positive PCR test, the clinical sites should bring the subjects back for repeat PCR testing as described below.
- The clinical sites should continue to collect PCR tests if a subject is experiencing possible COVID-19 symptoms, or had possible exposure to SARS-CoV-2 (ie, close contact tests positive for SARS-CoV-2). Testing will occur every 2 weeks for a total of 4 weeks (if 2 consecutive negative tests) or until negative (x2) after a positive result. Positive results will be reported as an AESI (Section 8.2.2) and subjects followed for disease severity, duration, and outcome.

Telephone visits will be conducted to augment the in person visits through 6 months post-vaccination (Table 1-1). CRU staff will interview the subjects about any potential exposure to the virus. If a subject has had potential exposure, the CRU will ask the subject to come in for an unscheduled visit that will include a nasopharyngeal swab.

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Subjects will be reminded at onsite visits and during telephone visits to contact the clinical site any time there is potential exposure to SARS-CoV-2 or they are experiencing any respiratory disease/symptoms suggestive of SARS-CoV-2 infection.

7.7 Safety Assessments

7.7.1 Adverse Events

Subjects will be monitored for AEs according to Section 8.

If a subject experiences respiratory symptoms suggestive of SARS-CoV-2 infection, the subject should notify the clinical site for a visit to collect nasopharyngeal swabs for RT-PCR virus detection.

Subjects with positive ELISA anti-N IgG results without COVID-19 symptoms may indicate asymptomatic SARS-CoV-2 infection and will be followed with the appropriate standard of care. Subjects with a positive ELISA anti-N IgG result should have a PCR test and be followed until both are negative as in the protocol instructions (Section 7.6).

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7.7.2 Reactogenicity Assessments

Subjects will keep a Diary Card to track reactogenicity assessments for 7 days after each vaccination. Reactogenicity assessments include generalized symptoms such as headache, fatigue, muscle pain, joint pain, nausea, chills, fever, and rash (not at injection site), and localized reactions including pain, erythema, induration, and swelling. If an AE continues after 7 days, the AE will be captured as ongoing/continuing (not noted as a new AE).

7.7.3 Laboratory Tests

A certified laboratory will be utilized to process and provide results for the clinical safety laboratory tests listed in Table 7-1. The baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the first dose of study vaccine.

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Subjects will fast a minimum of 8 hours prior to clinical laboratory sample collection at screening.

During the screening period, if a subject has an out-of-range value for a clinical safety laboratory parameter that the Investigator believes is not clinically significant or the Investigator does not believe is correct (eg, lab or specimen processing error), but the Investigator wants to confirm with a repeat laboratory test, a single repeat is allowed to confirm the initial result.

If Part C Expansion (optional) is performed, all Part C subjects will have safety laboratory tests performed at screening only in order to satisfy the inclusion/exclusion criteria. In addition, the first 200 subject in Part C will have safety laboratory tests performed at all time points. The remaining subjects in Part C will not have safety laboratory tests performed at any of the post-dose time points unless the Investigator deems it necessary.

Additional safety laboratory tests may be conducted as needed by the Investigator to evaluate subject safety.

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Table 7-1 Clinical Safety Laboratory and Screening Tests

Hematology	Chemistry		Urinalysis
Hematocrit Hemoglobin Red blood cell count White blood cell count Neutrophils (absolute) Lymphocytes (absolute) Monocytes (absolute) Basophils (absolute) Eosinophils (absolute) Platelet count (estimate not acceptable)	Albumin Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Gamma glutamyl transferase Direct bilirubin Total bilirubin Lactate dehydrogenase Total protein	Blood urea nitrogen Creatinine Calcium Phosphate Sodium Potassium Carbon dioxide Chloride Glucose [a] Total cholesterol Triglycerides [a]	Specific gravity Ketones pH Protein Blood Glucose Leukocyte esterase Microscopic analysis (performed if blood, leukocytes, or protein are present)
Urine Drugs of Abuse[b,c]	**Serology [d]**	**Other**	
Barbiturates Cocaine Tetrahydrocannabinol Amphetamines Opiates Phencyclidine	HIV-1 HIV-2 HBsAg HCV antibody	Prothrombin Pregnancy test Follicle-stimulating hormone [e] Alcohol screen[c]	

a. Fasting required at screening only
b. At a minimum, these tests must be included
c. During the screening period, urine drugs of abuse and alcohol screens may not be repeated for eligibility
d. Includes any confirmatory tests performed at the discretion of the Investigator
e. As needed to confirm postmenopausal status

For any laboratory test value outside the reference range that the Investigator considers clinically significant during the on-study period (ie, following dose administration), the Investigator will:

- Repeat the test to verify the out-of-range value and clinical significance.
- Follow the out-of-range value until the value returns to normal or baseline, or until the value is deemed stable and not clinically significant by the Investigator.
- Record as an AE any laboratory test value that is confirmed by repeat and the Investigator considers clinically significant, requires a subject to be discontinued from the study, requires a subject to receive treatment, or requires a change or discontinuation of the study vaccine (if applicable).

7.7.4 Vital Signs

Vital signs assessments will include systolic and diastolic blood pressure (mmHg), heart rate (bpm), respiratory rate (breaths per minute), and oral temperature (C°). In addition, oral temperature will be performed prior to each vaccination. Vital signs will be measured after the subject has been resting quietly in a seated position for at least 5 minutes. Any clinically significant abnormal vital sign assessment requires at least one repeat measurement.

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A vital signs abnormality that is considered clinically significant initially and on confirmation, requires a subject to be discontinued from the study, requires a subject to receive treatment, or requires discontinuation from the study vaccine (if applicable) will be recorded as an AE.

7.7.5 Physical Examination

Comprehensive physical examinations (excluding genital, rectal, and breast examinations [unless indicated]) will be performed, and abnormal findings will be documented in the subject's eCRF.

Targeted physical examinations will focus on any AEs ongoing at the time of the examination (Table 1-1).

An abnormal physical examination finding that is considered clinically significant and requires the subject to be discontinued from the study, requires the subject to receive treatment, or requires discontinuation of the study vaccine (if applicable) will be recorded as an AE.

7.7.6 Appropriateness of Safety Assessments

Safety evaluations selected for this study are typical of those for this subject population and utilize widely accepted measures.

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8 ADVERSE EVENTS

An AE is defined as any untoward medical occurrence in a subject administered a pharmaceutical product during the course of a clinical investigation. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a study vaccine, whether or not thought to be related to the study vaccine. A TEAE is any AE that occurs after the first dose of study drug, regardless of relationship to the study drug.

MAAEs are AEs for which the subject has received medical attention by medical personnel, or in an emergency room, or which led to hospitalization. For each reported AE, the Investigator will ask the subject if such medical attention has been received. In addition, the Investigator will assess each MAAE if it constitutes a NOCD, defined as a MAAE that was:

- absent at baseline,
- not resolved at EOS
- required continuous medical care or attention.

Subjects will be monitored throughout the study for AEs, from the first dose of study vaccine through Day 43 of the study and for SAEs, MAAEs, NOCDs, and AESIs from the first dose through the end of the study (Day 365 ±14 days). Adverse events that are identified at the last assessment visit (or the early termination visit) as specified in the protocol must be recorded on the AE eCRF with the status of the AE noted. All events that are ongoing at this time will be recorded as ongoing on the eCRF. All (both serious and nonserious) AEs must be followed until they are resolved or medically stable, or until reasonable attempts to determine resolution of the event are exhausted. The Investigator should use his/her discretion in ordering additional tests as necessary to monitor the resolution of such events.

The procedures specified in Section 8.4 are to be followed for reporting SAEs.

8.1 Recording Adverse Events

Adverse events are to be recorded on the AE page of the eCRF. The following information will be recorded:

- Assessment of whether or not the AE is an SAE, MAAE, NOCD, or AESI (Section 8.2.1)
- Assessment of AE intensity (Section 8.2.2)
- Assessment of AE relationship to study vaccine (Section 8.2.4)
- Action taken - dose not changed, vaccine dose 2 not given, not applicable, or unknown, as applicable
- Outcome - recorded as fatal, not recovered/not resolved, recovered/resolved, recovered/resolved with sequelae, recovering/resolving, or unknown, as applicable

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8.2 Assessment of Adverse Events

The Investigator will assess each AE for seriousness, intensity, and relationship to study vaccine.

8.2.1 Serious Adverse Events, Medically Attended Adverse Events, New Onset Chronic Medical Conditions, Adverse Events of Special Interest, and Potential Immune-mediated Conditions

The Investigator is responsible for determining whether an AE meets the definition of an SAE, MAAE, NOCDs, or AESIs including potential immune-mediated medical condition from the first dose of the study vaccine through the end of the study (Day 365 ±14 days).

An SAE is any AE that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

MAAEs are defined as hospitalization, an emergency room visit, or an otherwise unscheduled visit to or from medical personnel for any reason.

NOCDs are defined as any new ICD diagnosis (per current International Statistical Classification of Diseases and Related Health Problems) that is applied to the subject during the course of the study, after receipt of the study agent, that is expected to continue for at least 3 months and requires continued health care intervention.

AESIs are defined in Section 8.2.2 and a list of potential immune-mediated medical conditions is provided in Appendix B.

Note: SAEs, MAAEs, NOCDs, and AESIs including potential immune-mediated medical conditions require immediate reporting to the medical monitor and/or Sponsor. Refer to Section 8.4 for details.

8.2.2 Adverse Events of Special Interest

An AESI is any AE that a regulatory authority has mandated be reported on an expedited basis (including to the iSRC), regardless of the seriousness, expectedness, or relatedness of the AE to

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the administration of investigational product. To date, no AESIs have been identified specifically for the TAP-COVID-19 vaccine + CpG adjuvant. However, subjects who test positive for COVID-19, present with autoimmune disease, or are diagnosed with a potential immune-mediated medical condition (Appendix B) should be reported as AESI.

AESIs will be followed as per the procedures in the study protocol, SRM, and/or SAE SSP for SAEs and pregnancy reporting, regardless of the seriousness, expectedness, or relatedness of the AESI to the administration of study vaccine. AESIs will be reported by the site directly to the Sponsor, medical monitor, and SAE hotline at ICON (ICON Pharmacovigilance) (Section 8.4).

Subjects positive for SARS-CoV-2 will not be discontinued. Positive SARS-CoV-2 cases will be followed and include referral to a primary care physician, collection of all medical records, assessment of severity, and review by the site investigator and medical monitor. All positive SARS-CoV-2 cases will also be shared with the iSRC on an ongoing basis.

8.2.3 Intensity

The intensity of an AE will be graded according to Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (September 2007). The grading scale is comprised of 4 levels: mild (Grade 1), moderate (Grade 2), severe (Grade 3), and potentially life-threatening (Grade 4). For those AEs that are not covered in the Guidance for Industry (above) the rating scale from DAIDS (Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1) will be used (Table 8-1).

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Table 8-1 DAIDS Adverse Events Intensity Assessment

Grade	Intensity	Definition
Grade 1	Mild	Symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated.
Grade 2	Moderate	Symptoms causing greater than minimal interference with usual social and functional activities with intervention indicated.
Grade 3	Severe	Symptoms causing inability to perform usual social and functional activities with intervention or hospitalization indicated.
Grade 4	Potentially Life-Threatening	Symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death.
Grade 5		Any AE where the outcome is death

8.2.4 Relationship to Study Vaccine

The relationship of an AE to the study vaccine should be determined by the Investigator according to the following criteria:

- Not related: The event is most likely produced by other factors such as the subject's clinical condition, intercurrent illness, or concomitant drugs, and does not follow a known response pattern to the study vaccine, or the temporal relationship of the event to study vaccine administration makes a causal relationship unlikely

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- Related: The event follows a reasonable temporal sequence from the time of drug administration, and/or follows a known response pattern to the study vaccine, and cannot be reasonably explained by other factors such as the subject's clinical condition, intercurrent illness, or concomitant drugs

8.3 Discontinuation Due to Adverse Events

Any subject who experiences an AE may be withdrawn at any time from the study at the discretion of the Investigator. Subjects withdrawn from the study due to an AE, whether serious or nonserious, may be followed by the Investigator until the clinical outcome of the AE is determined. The subject will also be asked to participate in a Follow-up Visit at approximately Day 365 to check safety and immunogenicity. The AE(s) should be noted on the appropriate eCRFs, the subject's progress should be followed until the AE is resolved or medically stable as determined by the Investigator, and the Sponsor notified.

8.4 Reporting Serious Adverse Events and Adverse Events of Special Interest

In the event of any SAE or AESI reported or observed during the study, whether or not attributable to the study vaccine, site personnel will report it immediately by telephone to the Sponsor, medical monitor, AND SAE hotline at ICON (ICON Pharmacovigilance) in accordance with procedures described in the SRM and/or SAE SSP. Site personnel will follow up with a written report on the next working day.

Report Forms will be provided to the CRU to assist in collecting, organizing, and reporting SAEs or AESIs and follow-up information.

All SAEs and AESIs should be followed to their resolution, with documentation provided to the Sponsor/ICON on a follow-up Report Form.

8.5 Pregnancy

Pregnancies will be captured if they occur in female subjects from the time the subject is first exposed to the study vaccine until EOS. Pregnancies in the sexual partners of male subjects will be captured from the time the subject is first exposed to the study vaccine until 90 days after last exposure to the study vaccine.

Female subjects must be instructed to inform the study Investigator immediately if they become pregnant during the study.

The Investigator must report any pregnancy to the medical monitor, Sponsor, and ICON Pharmacovigilance within 1 business day of becoming aware of the pregnancy per pregnancy reporting procedures described in the SRM. The subject must be immediately discontinued from further treatment with study vaccine. An uncomplicated pregnancy will not be considered an AE or SAE; however, all pregnancies will be followed through birth and 3 months postdelivery.

Any congenital abnormalities in the offspring of a subject who received study vaccine will be reported as an SAE. The outcome of any pregnancy and the presence or absence of any congenital

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abnormality will be recorded in the source documentation and reported to the Sponsor and ICON Pharmacovigilance.

8.6 Drug-induced Liver Injury

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Subjects will be monitored for signs of DILI. Study vaccine (dose 2) will be withheld in the event of potential DILI.

Potential events of DILI will be defined as meeting all of the following criteria (as specified in the FDA Guidance for Industry Drug-induced Liver Injury: Premarketing Clinical Evaluation, 2009):

- ALT or AST >3 × ULN
- Total bilirubin >2 × ULN without initial findings of cholestasis (elevated serum ALP)
- No other reason can be found to explain the combination of laboratory value increases (eg, acute viral hepatitis; alcoholic and autoimmune hepatitis; hepatobiliary disorders; nonalcoholic steatohepatitis; cardiovascular causes; concomitant treatments)

Potential events of DILI will be reported as SAEs (Section 8.4). All subjects with potential DILI will be closely followed until abnormalities return to normal or baseline or until reasonable attempts to determine resolution of the event are exhausted.

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9 STATISTICAL CONSIDERATIONS

The statistical analysis will be conducted following the principles as specified in ICH Topic E9 (CPMP/ICH/363/96).

All statistical analyses will be described in a separate SAP.

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The statistical evaluation will be performed using SAS® software version 9.4 or higher (SAS Institute, Cary, NC). All data will be listed, and summary tables will be provided. No formal significance testing will be performed. Summary statistics will be presented by treatment group and include subset analysis (eg, all subjects, seronegative subjects [ie, neutralizing antibody titer < 10 at screening], seropositive subjects, and subjects that received an FDA Emergency Use Authorization/licensed COVID vaccine). For continuous variables, data will be summarized with the number of subjects, mean, standard deviation, median, minimum, maximum, geometric mean, CV%, GeoCV%, and 95% CI by treatment group. For categorical variables, data will be tabulated with the number and proportion of subjects for each category by treatment group.

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The database will be locked and unblinded after the data have been monitored for all subjects through Day 43. Details of the unblinded interim analysis are presented in Section 9.5.

The final analysis of the safety and immunogenicity data collected from Day 43 through Day 365/approximately 1 year after first vaccination will be performed after the study is completed. An addendum to the initial CSR will be prepared with data from final analysis. Details of the statistical analyses, methods, and data conventions will be described in the SAP.

Deleted: statistical analysis plan.

9.1 Sample Size Calculation

Deleted: An iSRC will be established by the Sponsor to monitor overall study conduct and to review accumulating safety data including immunogenicity at Day 43 for Part A and for Part B in both dose groups and throughout the study. The iSRC will also convene to monitor any Study Halting Rules or safety issues. ¶

No formal sample size calculation was performed.

A total of 180 subjects will be enrolled in Parts A and B. Approximately 90 eligible subjects (aged 18-49 years), with 30 subjects per treatment group for Part A and 90 eligible subjects (aged 50-85 years), with 30 subjects per treatment group for Part B, will be enrolled in the study.

An optional Part C Expansion may be conducted to confirm the safety and immunogenicity of the selected dose of vaccine in up to 1000 adult subjects randomized 1:1 (single dose level of study vaccine:placebo). The proposed sample size was selected based on WHO guidelines on clinical evaluation of vaccines: regulatory expectations Annex I (2001), which states that approximately 300 subjects are needed to identify common local reactogenicity events. A larger sample size will assist in a better characterization of kinetics and range of immunity (neutralizing antibody titers) and provide a more reliable output of seropositivity and seroconversion to TAP-COVID-19 immunization. With the limited clinical experience with SARS-CoV-2 vaccines and the current lack of a biomarker correlate of protection, the generation of this larger data set is relevant to inform the design and implementation of a Phase 3 program.

9.2 Analysis Populations

Enrolled Population: All subjects who signed the ICF.

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Safety Population: All subjects who provide consent, are randomized, and receive any amount of study vaccine/placebo. The Safety Population will be used for the demographic, baseline characteristic, safety data summaries, and the analysis of primary endpoints such as occurrence of solicited local and systemic reactogenicity.

Per Protocol (PP) Population: Includes all subjects in the Safety Population who receive the assigned doses of the study vaccine/placebo according to protocol, have serology results, and have no major protocol deviations affecting the primary immunogenicity outcomes, as determined by the Sponsor before database lock and unblinding. Subjects that are immunized with an approved vaccine will be captured as a subset analysis of the PP Population at Days 90, 181, 273, and 365 based on the date of receiving an approved COVID-19 vaccine.

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Modified Intent-to-Treat (mITT) Population: Includes all subjects in the Safety Population who provide any serology data. The mITT Population will be used for the immunogenicity analysis.

9.3 Randomization

The overall randomization for the study will be 2:1 (active:placebo). Each Part (A and B) and treatment (low and high) will be randomized individually 2:1 (active to placebo).

The study will start with Part A (18-49 years) low dose, randomized in a 2:1 ratio (30 subjects active:15 subjects placebo) for Treatment A (15 µg TAP-COVID-19 vaccine + 0.5 mg CpG).

Part A (18-49 years) high dose will be randomized in a 2:1 ratio (30 subjects active:15 subjects placebo) for Treatment B (45 µg TAP-COVID-19 vaccine + 0.5 mg CpG) after Part A low dose has completed enrollment and the iSRC has reviewed safety and tolerability data through Day 8.

Part B (50-85 years) low dose will be randomized in a 2:1 ratio (30 subjects active:15 subjects placebo) for Treatment A (15 µg TAP-COVID-19 vaccine + 0.5 mg CpG) after Part A low dose has completed enrollment and received the first vaccination and the iSRC has reviewed safety data through Day 8.

Part B (50-85 years) high dose will be randomized in a 2:1 ratio (30 subjects active:15 subjects placebo) for Treatment B (45 µg TAP-COVID-19 vaccine + 0.5 mg CpG) after Part B low dose has completed enrollment and received the first vaccination and the iSRC has reviewed safety data through Day 8.

A total of 90 subjects will be randomized in Part A (18-49 years); 30 subjects low dose (Treatment A, 15 µg TAP-COVID-19 vaccine + 0.5 mg CpG), 30 subjects high dose (Treatment B, 45 µg TAP-COVID-19 vaccine + 0.5 mg CpG), and 30 subjects placebo (Treatment C).

A total of 90 subjects will be randomized in Part B (50-85 years); 30 subjects low dose (Treatment A, 15 µg TAP-COVID-19 vaccine + 0.5 mg CpG), 30 subjects high dose (Treatment B, 45 µg TAP-COVID-19 vaccine + 0.5 mg CpG), and 30 subjects placebo (Treatment C).

Treatment A: TAP-COVID-19 vaccine (15 µg) + CpG (0.5 mg) IM injection on Day 1 and Day 22 (±3 days)

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Treatment B: TAP-COVID-19 vaccine (45 µg) + CpG (0.5 mg) IM injection on Day 1 and Day 22 (±3 days)

Treatment C: Placebo (buffered saline solution) IM injection on Day 1 and Day 22 (±3 days)

A computer-generated randomization schedule for each part (Part A, Part B, and Part C Expansion) will be generated prior to study start by an ICON biostatistician.

For sentinel dosing, 3 subjects from each part will be randomized 2:1 (active:placebo). The remainder of each cohort will also be randomized 2:1 (active:placebo).

9.4 Endpoints

Endpoints are presented in Section 3.2.

9.5 Interim Analyses

An unblinded interim analysis will be performed on the safety and immunogenicity data collected for each of the 4 dose groups (Part A low dose, Part A high dose, Part B low dose, and Part B high dose). Unblinded interim analysis will occur for the Part A low dose group (including active and placebo subjects) when the first 30 subjects vaccinated have data available from Day 1 through Day 43. The remaining cohorts will have an unblinded interim analysis performed when all subjects in the cohort have data from Day 1 through Day 43. For the interim analysis, treatment codes will be unblinded after the data are deemed ready for the analysis and the data has been monitored. The CRO [except for the unblinded team members preparing the data for unblinded iSRC review], Investigator, and clinical staff will not have access to the unblinded treatment group interim analyses and will remain blinded until completion of the study. The Sponsor will be unblinded at the interim analysis. Safety and immunogenicity analyses from this unblinded interim analysis will be presented in a CSR. This CSR may be submitted to regulatory authorities as needed.

9.6 Immunogenicity Analysis

The mITT Population will be used for all listings and summary statistics corresponding to immunogenicity analysis.

The individual sampling and blood collection for ELISA analysis to determine IgG and IgM antibody titers to the spike RBD and neutralizing antibody titers for parent (Wuhan) and any variant SARS-CoV-2 strains, will be listed and summarized by time points for each part by treatment.

All derived immunogenicity secondary endpoint parameters: GMT, GMT ratio, GMFR, GMI, and seroconversion rates will be listed and summarized by scheduled time point using descriptive statistics (n, mean, SD, minimum, median, maximum, geometric mean, CV%, GeoCV%, and 95% CI) for each part by treatment.

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PBMC and serum sample data for future research results at each scheduled visit will also be provided separately in a listing and summary table, if applicable.

Subgroup analysis for safety and efficacy will be performed for those subjects who were seropositive when enrolled.

Graphical display of the summary results or at individual time points will be provided as needed (eg, scatter plots of subject titer values to visually display individual data points).

Additional details for analysis of immunogenicity are presented in the SAP.

9.7 Cellular Analysis

The number of IFN-γ and IL-5 producing T-cells (CD4+ and CD8+) from PBMCs responsive to vaccine antigens will be listed and summarized by time point using appropriate descriptive statistics for each part by treatment.

Additional details for cellular analysis are presented in the SAP.

9.8 Safety Analysis

Safety Population will be used for all safety variables specified.

All safety data will be summarized by part and treatment. No statistical tests will be performed.

Subjects who are seropositive and seronegative at screening will also be summarized and safety and efficacy subgroup analysis will be performed for these groups of subjects.

Additional details for safety analysis are presented in the SAP.

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10 ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator will provide direct access to source data and documents for individuals conducting study-related monitoring, audits, IRB review, and regulatory review. The Investigator must inform the study subject that his/her study-related records may be reviewed by the above individuals without violating the subject's privacy of personal health information in compliance with HIPAA regulations.

Attention is drawn to the regulations promulgated by the FDA under the Freedom of Information Act providing, in part, that information furnished to clinical Investigators and IRBs will be kept confidential by the FDA only if maintained in confidence by the clinical Investigator and IRB. By signing this protocol, the Investigator affirms to the Sponsor that the Investigator will maintain, in confidence, information furnished to him or her by the Sponsor and will divulge such information to the IRB under an appropriate understanding of confidentiality with such board.

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11 QUALITY CONTROL AND QUALITY ASSURANCE

Sponsor/ICON will implement and maintain quality control and quality assurance procedures with written SOPs to ensure the study is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, and applicable regulatory requirements.

11.1 Conduct of Study

This study will be conducted in accordance with the provisions of the Declaration of Helsinki and all revisions thereof (Tokyo 2004), and in accordance with FDA CFR (§312.50 and §312.56) and the ICH E6 Guidelines on GCP (CPMP/ICH/135/95). Specifically, this study is based on adequately performed laboratory and animal experimentation; the study will be conducted under a protocol reviewed by an IRB; the study will be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the subjects will be respected; the physicians conducting the study do not find the hazards to outweigh the potential benefits; and each subject will give his or her written, informed consent before any protocol-driven tests or evaluations are performed.

The Investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate IRB, except when necessary to eliminate immediate hazards to the subject or when the change(s) involve only logistical or administrative aspects of the study and are approved by the Sponsor. Any deviation may result in the subject having to be withdrawn from the study, and may render that subject nonevaluable.

11.1.1 Protocol Deviations

A protocol deviation is defined as any intentional or unintentional change to, or noncompliance with, the approved protocol procedures or requirements. Deviations may result from the action or inaction of the subject, Investigator, or site staff.

At the outset of the study, a process for defining and handling protocol deviations will be established. This will include determining which violations will be designated "key," requiring immediate notification to the medical monitor and/or Sponsor. The Investigator is responsible for seeing that any known protocol deviations are recorded and handled as agreed.

11.2 Protocol Amendments

Only the Sponsor may modify the protocol. Amendments to the protocol will be made only after consultation and agreement between the Sponsor and the Investigator. All amendments that have an impact on subject risk or the study objectives, or require revision of the ICF, must receive approval from the IRB prior to their implementation.

11.3 Monitoring of Study

The Investigator will permit the CRA to review study data as frequently as is deemed necessary to ensure data are being recorded in an adequate manner and protocol adherence is satisfactory.

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The Investigator will provide access to medical records for the monitor to verify eCRF entries. The Investigator is expected to cooperate with the Sponsor or a designee in ensuring the study adheres to GCP requirements.

The Investigator may not recruit subjects into the study until the Sponsor or a designee has conducted a site initiation visit (in-person or via teleconference) to review the protocol and eCRF in detail.

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12 ETHICS

12.1 Institutional Review Board Approval

12.1.1 Ethics Review Prior to Study

The Investigator will ensure that the protocol and ICF are reviewed and approved by the appropriate IRB prior to the start of any study procedures. The IRB will be appropriately constituted and will perform its functions in accordance with FDA regulations, ICH GCP guidelines, and local requirements as applicable.

12.1.2 Ethics Review of Other Documents

The IRB will approve all protocol amendments (except for Sponsor-approved logistical or administrative changes), written informed consent documents and document updates, subject recruitment procedures, written information to be provided to the subjects, available safety information, information about payment and compensation available to subjects, the Investigator's curriculum vitae and/or other evidence of qualifications, and any other documents requested by the IRB and regulatory authority as applicable.

12.2 Written Informed Consent

The nature and purpose of the study will be fully explained to each subject. The subjects must be given ample time and opportunity to inquire about details of the study, to have questions answered to their satisfaction, and to decide whether to participate. Written informed consent must be obtained from each subject prior to any study procedures being performed.

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13 DATA HANDLING AND RECORD KEEPING

13.1 Data Reporting and Case Report Forms

13.1.1 Case Report Forms

The Investigator will be provided with eCRFs, and will ensure all data from subject visits are promptly entered into the eCRFs in accordance with the specific instructions given. The Investigator must sign the eCRFs to verify the integrity of the data recorded.

13.1.2 Laboratory Data

A list of the normal ranges for all laboratory tests to be undertaken forms part of the documentation to be collated prior to study start. If a central laboratory has been selected to conduct any or all tests, it is essential all samples be analyzed at that laboratory. The Investigator must maintain source documents such as laboratory reports and complete history and physical examination reports.

13.1.3 Retention of Source Documents

The Investigator must maintain source documents such as laboratory reports, x-rays, ECGs, consultation reports, and complete history and physical examination reports.

13.2 Retention of Essential Documents

The study essential documents must be maintained as specified in the ICH guidelines for GCP and the applicable regulatory requirements. The Investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study vaccine. These documents should be retained for a longer period; however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

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14 ADMINISTRATIVE INFORMATION

14.1 Financing and Insurance

Financing and insurance will be addressed in a separate agreement between the Sponsor and the Investigator.

14.2 Publication Policy

The Sponsor will retain ownership of all data. All proposed publications based on this study will be subject to Sponsor's approval requirements.

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16 SIGNATURES

Protocol Number: KBP-201

Protocol Title: A Phase I/II, First-in-human, Observer-blinded, Randomized, Placebo-controlled, Parallel Group Study to Evaluate the Safety and Immunogenicity of TAP-COVID-19 SARS-CoV-2 Vaccine with CpG Adjuvant in Healthy Adults Aged 18-49 and 50-85

Kentucky BioProcessing, Inc. Signatures

This clinical study protocol has been reviewed and approved by Kentucky BioProcessing, Inc.

Oscar (Tony) A. Guzman, MD, CP Clinical Project Lead	Date

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President

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Investigator Signature

I agree to conduct the aforementioned study according to the terms and conditions of the protocol, GCP guidelines, and all other applicable local and regulatory requirements. All information pertaining to the study will be treated in a confidential manner.

_____
Site Name

_____
Print Name

_____ _____
Signature Date

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APPENDIX A DIARY CARD EXAMPLE

Example Diary Card may be adjusted to add additional subject collection information or CRU and/or subject contact information.

VACCINE REACTION AND ADVERSE EVENT DIARY

Section 1: Diary - Reactogenicity Days 1-8

My Subject ID number is _____

Date								
Day of immunization ▶ / **Symptom**	Evening of Dose	1 Day after	2 Days after	3 Days after	4 Days after	5 Days after	6 Days after	7 Days after
Body temperature **Celsius (C) or Fahrenheit (F)**	°	°	°	°	°	°	°	°
Fill in today's column by entering the worst grade/severity for each symptom that you have had in the last day (24 hours). Symptom grades are defined at the bottom of the page.								
No Symptoms of Any Kind – Tick this box								
Generalized Symptoms								
Headache								
Fatigue								
Muscle Pain								
Joint pain								
Nausea								
Chills								
Feverish								
Rash (not at injection site)								
Local Reactions								
Pain								
Erythema / redness in mm								
Induration in mm								
Swelling in mm								
In addition, tick the box in today's column if your answer to the question below is YES.								
Any other new symptom(s)? Y or N. If yes, describe in section 2.								

Grade 0 =	I didn't have it at all.
Grade 1 =	I noticed it, but it didn't interfere with my usual activities at all.
Grade 2 =	I had it, and it was bad enough to prevent a significant part of my usual activities.
Grade 3 =	I had it, and it prevented most or all of my normal activities, or I had to see a doctor for prescription medicine.
Grade 4 =	I had to visit the ER or was hospitalized because of the specific symptom

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VACCINE REACTION AND ADVERSE EVENT DIARY

Section 2: Other Adverse Events

Please describe any other symptoms experienced beyond those listed above. Please describe symptom or diagnosis, severity, start and stop day, if you saw a health care professional and severity below.

Symptom or Diagnosis if visited a Health Care Provider	Did you visit a health care provider	Start Date	Stop Date	Severity[1]	Comments, including any medicine prescribed or taken to reduce the symptoms

[1]**Please use these qualitative definitions to grade your symptoms:**	
Grade 1 =	I noticed it, but it didn't interfere with my usual activities at all.
Grade 2 =	I had it, and it was bad enough to prevent a significant part of my usual activities.
Grade 3 =	I had it, and it prevented most or all of my normal activities, or I had to see a doctor for prescription medicine.
Grade 4 =	I had it and visited the ER or was hospitalized for it.

Please return this document to your study site.
If at any time you have questions about completing the diary card, your health, or about the study in general, please contact the study site personnel.

Study Site Contact Information:
Principal Investigator Name:
Study Coordinator/Point of Contact:
Phone #:
Email address:

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APPENDIX B POTENTIAL IMMUNE-MEDIATED MEDICAL CONDITIONS

Gastrointestinal Disorders

- Autoimmune pancreatitis
- Celiac disease
- Crohn's disease
- Microscopic colitis
- Ulcerative colitis
- Ulcerative proctitis

Liver Disorders

- Autoimmune cholangitis
- Autoimmune hepatitis
- Primary biliary cirrhosis
- Primary sclerosing cholangitis

Metabolic Diseases

- Addison's disease
- Autoimmune hypophysitis
- Autoimmune thyroiditis (including Hashimoto thyroiditis)
- Diabetes mellitus type I
- Grave's or Basedow's disease

Musculoskeletal Disorders

- Antisynthetase syndrome
- Dermatomyositis
- Juvenile chronic arthritis (including Still's disease)
- Mixed connective tissue disorder
- Polymyalgia rheumatic
- Polymyositis
- Psoriatic arthropathy
- Relapsing polychondritis
- Rheumatoid arthritis
- Scleroderma, including diffuse systemic form and CREST (alcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) syndrome
- Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome), and undifferentiated spondyloarthritis
- Systemic lupus erythematosus
- Systemic sclerosis

Neuroinflammatory Disorders

- Acute disseminated encephalomyelitis, including site-specific variants (eg, noninfectious encephalitis, encephalomyelitis, myelitis, radiculomyelitis)

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- Cranial nerve disorders, including paralyses/paresis (eg, Bell's palsy)
- Guillain-Barré syndrome, including Miller Fisher syndrome and other variants
- Immune-mediated peripheral neuropathies and plexopathies, including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy
- Multiple sclerosis
- Narcolepsy
- Optic neuritis
- Transverse myelitis
- Myasthenia gravis, including Eaton-Lambert syndrome

Skin Disorders

- Alopecia areata
- Autoimmune bullous skin diseases, including pemphigus, pemphigoid and dermatitis herpetiformis
- Cutaneous lupus erythematosus
- Erythema nodosum
- Morphoea
- Lichen planus
- Psoriasis
- Sweet's syndrome
- Vitiligo

Vasculitides

- Large vessels vasculitis including: giant cell arteritis such as Takayasu's arteritis and temporal arteritis
- Medium sized and/or small vessels vasculitis including the following:
  - Polyarteritis nodosa
  - Kawasaki's disease
  - Microscopic polyangiitis
  - Wegener' granulomatosis
  - Behcet's syndrome
  - Leukocytoclastic vasculitis
  - Henoch-Schonlein purpura
  - Necrotizing vasculitis and antineutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified)
  - Churg-Strauss syndrome (allergic granulomatous angiitis)
  - Buerger's disease thromboangiitis obliterans

Others

- Antiphospholipid syndrome
- Autoimmune hemolytic anemia

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- Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis)
- Autoimmune myocarditis/cardiomyopathy
- Autoimmune neutropenia
- Autoimmune pancytopenia
- Autoimmune thrombocytopenia
- Goodpasture syndrome
- Idiopathic pulmonary fibrosis
- Pernicious anemia
- Polyglandular autoimmune syndrome
- Raynaud's phenomenon
- Sarcoidosis
- Sjögren's syndrome
- Stevens-Johnson syndrome
- Uveitis

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APPENDIX C ADDITIONAL ELISA DETAILS

Name That Appears on Laboratory Report	Vendor	SARs-CoV-2 Antigen	Reporting Status	Intended Use
Anti-SARS-CoV-2 IgG Qual	Euroimmun	Spike (S)	Blinded starting at the Day 1 Visit	It is intended for use as an aid in identifying individuals with an adaptive immune response to SARS-CoV-2, indicating recent or prior infection. At this time, it is unknown for how long antibodies persist following infection and if the presence of antibodies confers protective immunity. This test should not be used to diagnose acute SARS-CoV-2 infection.
SARS-CoV-2 IgG Qual	Abbott Architect	Nucleocapsid (N)	Unblinded throughout the duration of the study	This assay is designed to detect immunoglobulin class G (IgG) antibodies to the nucleocapsid protein of SARS-CoV-2 in serum and plasma from individuals who are suspected to have had COVID-19 or in serum and plasma of subject that may have been infected by SARS-CoV-2.
COVID-19 IgM	Epitope Diagnostics	Nucleocapsid (N)	Unblinded throughout the duration of the study	This test is used as an aid for the detection of novel COVID-19.

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Page 2: [1] Formatted	Aragon, Stacie	11/12/2021 2:45:00 PM

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