Anlage zum inhaltlichen Mängelschreiben des Paul-Ehrlich-Instituts vom 16.04.2020

Prüfsubstanz: BNT162
EudraCT-Nr.: 2020-001038-36
Vorlage-Nr.: 4069/01

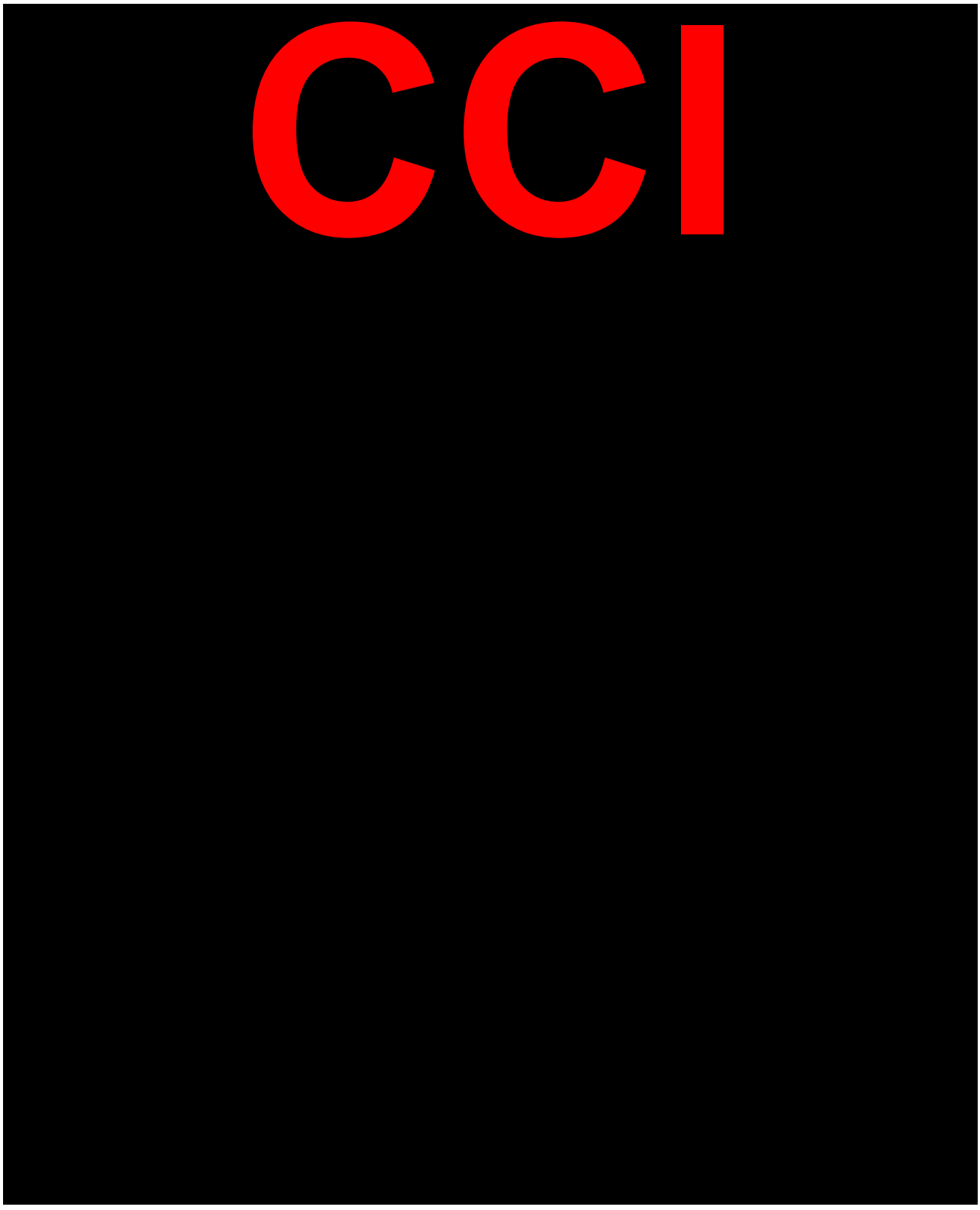
Titel der klinischen Studie: Protocol Title: A Multi-site, Phase I/II, 2-Part, Dose-Escalation Trial Investigating the Safety and Immunogenicity of four Prophylactic SARS-CoV-2 RNA Vaccines Against COVID-2019 Using Different Dosing Regimens in Healthy Adults

General:

Es wird darum gebeten im EMA-Antragsformular / in der XML-Datei unter dem Punkt E 1.2 "MedDRA version, level, term and classification code" entsprechende Angaben einzufügen. Das EMA-Antragsformular/die XML-Datei sind entsprechend zu aktualisieren

Quality Part:

CCI



Clinical Part:

Definition of seroconversion (Objectives):

18 Seroconversion is defined as a minimum of 4-fold increase of antibody titers as compared to baseline at 7±1 d, 21±2 d, 42±3 d, 84±5 d, and 183±7 d after the primary immunization. The applicant is asked to identify the cut-off values of the serological assays used and to clarify which titer will be applied as indicator of sero-negativity.

Discrimination between vaccinated and infected subjects

19 PCR-based testing for SAR-CoV-2 as an eligibility criterion and testing for anti-SARS-CoV- 2 antibodies as baseline reference for immunogenicity analysis will be performed before day 0. This is described in section 8.2.10, and is endorsed. The applicant is asked to consider establishing testing to discriminate between vaccinated and infected subjects. This should be reflected in the protocol.

Dosing of cohorts 2 and 4 (page 27)

20 The data assessed by the SRC to allow dosing in cohort 2 and cohort 4 comprises 48 h data for 6 subjects (including observation on site, phone interview (if available), vital signs, TEAEs, local reactions, blood/clinical laboratory data, and brief physical examination outcome).The applicant is asked to clarify what “if available” means.

Intermediate dosing groups (page 8)

21 On page 8 is stated: Part A has four cohorts (one per dose level), each with four planned groups (1A for BNT162a1, 1B for BNT162b1, 1C for BNT162b2, and 1D for BNT162c1) and two optional groups (1E, 1F, etc.). For details, see Table 1. Table 1 however does not include information on the optional groups. The dosing in the two optional groups appears not yet specified. To archive flexibility this is acceptable as long as no higher doses, than the currently specified ones will be given. The applicant is asked to provide information on the optional dosing groups 1E and 1F (when to be given, decision making, etc). These information should be given in in the text on page 8 and/or in table 1, since the text refers to table 1. Otherwise these two dosing groups have no context and are confusing.

Description of part B trial design (page 6)

22 The design of part B is not finalised yet. The applicant should keep in mind, that a randomised placebo controlled trial design for part B is considered mandatory.

On page 6 of the CTP it is stated, that Part B **may** use a randomized, placebo-controlled, design. The applicant is asked to change **may use** into **will use**.

Before initiation of part B, a protocol amendment is needed with detailed description of endpoints, randomisation/blinding (if applicable) procedures, the sample size rationale, and the planned statistical analyses.

Progression to part B shall be based on sound analysis of immunogenicity and safety data gathered during part A.

Risk assessment section 2.3.1/2/3

23 The risk assessment provided by the applicant is in principle endorsed, but the theoretical concern of ADE should briefly be mentioned and described.

Follow of enhanced respiratory disease

24 The applicant should evaluate options to follow up subjects for enhanced respiratory disease through end of trial and include them into protocol if possible (e.g. as AESI).

Informed consent procedure section 10.1.3

25 Trial participants should be informed about the theoretical risk of ADE/RDE.

The applicant is asked to include this into the IC procedure.

Section 6.6.1 Dose limiting toxicity

26 Are the criteria in section 6.6.1 identical to stopping criteria for the trial? The applicant is asked to either refer from section 6.6.1 to section **6.6.4 safety stopping criteria** and verse vice, since there are no specific stopping criteria mentioned in section 6.6.4, or define specific stopping rules in section 6.6.4.

Note to applicant:

Section 10.1.5 Committees – SRC

In this section it is stated:

Before progression to Part B, review and evaluate at least the Day 21 data per vaccine to decide whether to progress to Part B, and if yes, define what doses will be given.

The data assessed by the SRC comprises: (Data for 6 subjects collected up to and including Visit 3) vital signs, TEAEs, local reactions, blood/clinical laboratory data, brief physical examination outcome, and immunogenicity.

The importance of combining safety and immunogenicity data for dose selection for part B was stressed by PEI during SA TCs and written feedback on preliminary trial protocol.

Progression to part B shall be based on sound analysis of immunogenicity and safety data gathered during part A.

Zur Information: Grundsätzlich können Statements/ Commitments /Versprechen nicht als formal abschließende Antwort auf Mängelpunkte akzeptiert werden, da solche Zusagen rechtlich nur sehr eingeschränkt bindend sind.
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