CONFIDENTIAL

STATISTICAL ANALYSIS PLAN

A Randomized, Open label, Single Centre, Phase 2 Trial of the Malaria Vaccine, R21/Matrix-M™, to Assess Safety and Immunogenicity of the vaccine in Thai Adults

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1 INTRODUCTION

This study is a randomized, open-label, single centre, Phase 2 trial of R21/Matrix-M™. A total of 120 healthy non-pregnant Thai adults, aged 18-55 years, inclusive, will be enrolled and randomised to one of three study groups:

- Arm 1: R21/Matrix-M™ in subjects who concurrently receive co-formulated dihydroartemisinin/piperaquine + single low dose of primaquine (SLDPQ).
- Arm 2: R21/Matrix-M™ alone.
- Arm 3: Co-formulated dihydroartemisinin/piperaquine + SLDPQ

We propose to conduct a safety and immunogenicity trial of R21/Matrix-M™. The major aims of this study are to: (1) assess the safety and immunogenicity of R21/Matrix-M™ in healthy Thai adults, (2) confirm that the co-administration of antimalarial drugs with R21/Matrix-M™ does not reduce the immunogenicity of the vaccine, and (3) assess the pharmacokinetics of antimalarial drug: piperaquine in subjects who concurrently receive R21/Matrix-M™. This study will contribute to our understanding of the immunogenicity of a vaccine, which could potentially be used to help stop the spread of malaria and anti-malarial resistance in the region.

2 BACKGROUND INFORMATION

2.1 OBJECTIVES

2.1.1 PRIMARY OBJECTIVES

- To assess the safety of the R21/Matrix-M™ vaccine, with and without concurrent anti-malarial administration, in Thai adults.

2.1.2 SECONDARY OBJECTIVES

- To compare the immunologic response to R21/Matrix-M™ vaccine when concurrently given with DHA-PIP + SLD-PQ (Arm 1) with R21/Matrix-M™ vaccine alone (Arm 2) in Thai adults.
- To compare the piperaquine levels of participants who received the antimalarial drugs alone (Arm 3) with participants who received the antimalarial drugs combined vaccine (Arm 1).

2.1.3 STUDY DESIGN

This study is a randomized, open-label, single centre, Phase 2 trial of R21/Matrix-M™. A total of 120 healthy non-pregnant Thai adults, aged 18-55 years, inclusive, will be enrolled and randomised to one of three study groups:

- Arm 1: R21/Matrix-M™ in subjects who concurrently receive co-formulated dihydroartemisinin/piperaquine + single low dose of primaquine (SLDPQ).
- Arm 2: R21/Matrix-M™ alone.
- Arm 3: Co-formulated dihydroartemisinin/piperaquine + SLDPQ

2.1.4 PATIENT POPULATION

Healthy Thai adults aged 18-55 years.

The inclusion and exclusion are detailed in the protocol section B5.

2.1.5 SAMPLE SIZE

The sample size calculations are based on the objective of comparing the serologic response to R21/Matrix-M™ vaccine concurrently given with DHA-PIP + SLD-PQ with R21/Matrix-M™ vaccine alone in adults instead of basing it on safety outcome. This is a Phase II trial. Sample sizes for Phase II trials are usually small, as safety is still of paramount importance. Because of this limitation, these phase II studies are usually powered on the immunogenicity/efficacy endpoints because safety events are rare and a sample size based on safety would lead to a very high sample size that would not be acceptable from ethical standpoint. Another reason why powering it on immunogenicity/efficacy (a co-primary objective) is important, is that if the vaccine has a poor immunogenicity profile then the safety question becomes redundant unless the study is a non-inferiority trial. We are optimistic that this sample size will be able to reveal important safety signals between arms which can be further explored in a phase III trial. The efficacy endpoint (Immunogenicity objective) is a co-primary objective to the safety objective. We include both "safety" and "immunogenicity" terms in the study title because both of them are key endpoints**.** Valid sample sizes for comparing sample sizes between two groups are usually obtained using exact test methods such as the Fisher's exact test power calculations. This is done using simulations as sample size formulas are not well developed. To estimate the sample size we use a four-fold increase in anti –CS antibody titre as an assumed correlate of protection. For the sample size calculation, we assume that the background rate of response in the reference groups will be 5% and the true rate of anti-CS antibody response in the vaccine groups is 80%. We wish to exclude, for the vaccine, a one-tailed lower 95% CI for the reference-vaccine group difference of lower than 30%. The study aims to detect this difference with at least 90% power (because the detectable difference is big) and testing at 5% significance level. Based on these assumptions and using the method of Blackwelder for precision-based sample size calculations, a total of 20 participants per arm would be needed for arm 3 to test against each of arms 1 and 2 separately because the anticipated difference is too big. However, for arms 1 and 2 (Table 1 below), we will need more participants per group because a smaller detectable effect is anticipated. Using the Fisher's exact test power simulations, a difference in serologic response of 30% (say 50% vs 80%) gives more than 80% power (i.e. 85% power) with a sample size of 50 participants in each of arms 1 and 2 testing at 5% significance level. Therefore, the total sample size for all the 3 arms will be 120 participants. The size of study groups is relatively small hence it is imperative to minimise potential losses. Whenever possible an attempt will be made to replace study participates should a participant be withdrawn or choose to withdraw. The stata command for obtaining the Fishers exact test power simulations is: power two proportions 0.50 0.80, test(fisher) n1(50) n2(50). This has been performed in Stata 16. The required sample sizes are summarized as follows:

Table 1. Sample size and vaccine vials required for each arm

Group	# Participants	Vaccine	Dose M0	Dose M1	Dose M2	Vaccine vials required
1	50	R21/Matrix-M™	Single standard dose (0.75mL)	Single standard dose (0.75mL)	Single standard dose (0.75mL)	300
2	50	R21/Matrix-M™	Single standard dose (0.75mL)	Single standard dose (0.75mL)	Single standard dose (0.75mL)	300
3	20	No vaccine	No vaccine	No vaccine	No vaccine	0
Total	120					600

Remark: R21/Matrix-M™ = adult formulation containing 10 µg of R21 and 50 µg Matrix-M in the standard dose of 0.75mL.

2.1.6 RANDOMISATION

Randomization numbers will be generated in blocks, for the 3 study arms in a ratio of 5:5:2, as follows:

- R21/Matrix-M™ + DHA-PIP+PQ (Arm 1)
- R21/Matrix-M™ alone (Arm 2)
- DHA-PIP+PQ alone (Arm 3)

Study participants will be assigned the next available randomization number on the list, and thus will be randomly allocated to Group 1, 2, or 3. This is an open-label study. Participants and clinical investigators will not be blinded to group allocation.

3 ANALYSIS OF PRIMARY AND SECONDARY OUTCOMES

3.1 INCLUSION IN ANALYSIS

All patients who received at least one dose of vaccine will be included in the safety analyses. Patients lost to follow-up before the completion of the follow-up period assessments will be censored at the last day seen.

Exclusion

Given the incidence of malaria in the study area, it is highly unlikely that any volunteer became infected with any *Plasmodium* species during the trial. However, to exclude the remote possibility that a participant becomes infected we will screen participants for malaria at the time screening, Month 0, Month 1, Month 2, Month 3, and Month 6. The malaria screen consists of a RDT. The result will be available in <30 min. Subjects positive for malaria at screening or Month 0 will be excluded from participation in the study and will not be enrolled or vaccinated. Subjects positive for malaria at Month 1 or Month 2 would be withdrawn from further vaccinations. In the remote scenario that a volunteer becomes parasitaemic during the study results obtained from that point in time onward will be confounded by the immune response to the natural infection. Immunology results obtained during and after an episode of parasitaemia will be excluded from the immunology analysis. The results will be included in the safety analysis.

The results will be reported in two ways: a) excluding results for the out-of-window visit as specified in the protocol (analogous to the per protocol approach PP) and b) including the results analogous to an intention to treat ITT approach.

3.2 PRIMARY OUTCOME

The primary outcome measures will be:

- The safety of the investigational treatment in each group:
    - Occurrence of serious adverse events (SAEs) from the date of the first vaccination to 28 days after the last vaccination, according to the MedRA classification.
    - Occurrence of SAEs during the whole study period, i.e. during a 6 month follow up period from the receipt of first vaccination, according to the MedRA classification.
- For all the 3 groups, the concentration of antibodies against *Plasmodium falciparum* circumsporozoite (anti-CS antibody), one month after the first dose (at Study month 1), one month after the second dose (at Study month 2).

4 STATISTICAL METHODS

4.1 GENERAL CONSIDERATIONS

4.1.1 DATA CHECKS

Data for each variable including calculated changes from baseline will be summarised using descriptive statistics such as n, mean, median, minimum and maximum, to check for any values that are out of range

or implausible. Missing data will be identified and queried when preparing data for analysis.

4.1.2 BASELINE DATA

Patient demographic characteristics (age, gender, weight), and all other baseline information will be summarised for each treatment group.

Numbers (with percentages) for binary and categorical variables. The mean (standard deviation) will be presented for continuous normally distributed data. The median (interquartile or full range) for continuous variables will be presented. Highly skewed data that take a wide range of values (including very large values) will be log transformed for meaningful analyses.

There will be no tests of statistical significance conducted for differences between randomised groups on any baseline variables.

4.1.3 SCREENING AND RECRUITMENT FLOWCHART

A study flowchart showing numbers of participants screened, randomised and those who are available for the final analysis populations will be constructed. Reasons for drop-out or exclusions will be shown at each stage.

4.1.4 ANALYSIS POPULATION

Primary outcome analyses will be carried out on both the according to protocol (PP) and the intention to treat (ITT) population. The PP analyses will be the main strategy for the immunogenicity analyses. The safety outcomes will be ITT. In the event of some subjects not meeting the in-/exclusion criteria at baseline being erroneously enrolled in the study, a modified intention to treat analysis (mITT) will be considered. In that case, reasons for exclusions will be clearly documented and justified. In the intention-to-treat analysis, every participant randomized in the study (who receive the correct or incorrect study agent, one or more doses, and complete or incomplete doses) will be analysed, except if he/she did not receive any dose of the study vaccine or if no post-randomization data was collected for this participant.

The per-protocol analysis will compare participants according to the study agent/treatment actually received and will include only those participants who satisfied the inclusion/exclusion criteria, followed the protocol, and received complete, correct doses. The following non-compliant participants will be excluded:

- Participants included without meeting at least one inclusion criterion
- Participants included despite meeting at least one exclusion criterion
- Participants found non-compliant with the blood sampling schedule
- Participants vaccinated with the wrong study agent (non-compliance with the randomization code)
- Participants excluded from the intention-to-treat (mITT) analysis.

4.1.5 ANALYSES TO ADDRESS PRIMARY AND SECONDARY OBJECTIVES

4.1.6 DESCRIPTIVE ANALYSES

For each study measure descriptive statistics within each randomised group and overall will be presented for data at each study time point.

Table 2. –Characteristics (M0 Day 0 measurements) of the participants by vaccine group

Characteristic	R21/Matrix-M™ + DHA-PIP + SLD-PQ **n=X**	R21/Matrix-M™ **n=X**	**No Vaccine n=X**
Gender n (% male)			
Age (years): median (range)			
Weight (kg): median (range)			
QTc int (msec): median (range)			
Fever n (%)			
Hb mean (sd)			
WBC median (range)			
Platelets median (range)			
Creatinine median (range)			
AST median (range)			
ALT median (range)			
Temperature mean (sd)			

4.1.7 ANALYSIS OF IMMUNOGENICITY

The serum anti-CS antibody titre and avidity responses for each treatment arm will be compared to the titre before vaccine administration as outlined in tables 2a, 2b, 3a and 3b below. In addition, immunology will be analyzed and compared in terms of the potential parameters using appropriate statistics according to the data structure in which data will be presented to the statistician. While the final choice of immunologic assays will be determined at a later stage the may include the following:

- *Plasmodium falciparum*. Circumsporozoite Protein. (NANP)6 Ab.IgG
- *Plasmodium falciparum*. Circumsporozoide Protein. (NANP)6 Ab.IgG Avidity
- *Plasmodium falciparum*. anti-C-Term Circumsporozoide Ab.IgG
- *Plasmodium falciparum*. anti-C-Term Circumsporozoide Ab.IgG avidity
- *Plasmodium falciparum*. Circumsporozoite Full length (N+C-Terminal)
- *Plasmodium falciparum*. anti-full length CSP Ab.IgG avidity

The serum anti-CS antibody titre -Proportion in study group with >4-fold rise in titre from baseline to: One month after first dose; One month after second dose; One month after the third dose; Six Months after the first dose for all groups.

Table 3ai. *Plasmodium falciparum*. Circumsporozoite Protein.(NANP)6 Ab.IgG

ARM	1 month after 1st dose **n (%)**	1 month after 2nd dose **n (%)**	1 month after 3rd dose **n (%)**	6 months after 1st dose **n (%)**
R21/Matrix-M™ + DHA-PIP + SLD-PQ				
R21/Matrix-M™				
No vaccine				

Table 3aii. *Plasmodium falciparum*. anti-C-Term Circumsporozoide Ab.IgG

ARM	1 month after 1st dose **n (%)**	1 month after 2nd dose **n (%)**	1 month after 3rd dose **n (%)**	6 months after 1st dose **n (%)**
R21/Matrix-M™ + DHA-PIP + SLD-PQ				
R21/Matrix-M™				
No vaccine				

Table 3aiii. *Plasmodium falciparum*. Circumsporozoite Full length (N+C-Terminal)

ARM	1 month after 1st dose **n (%)**	1 month after 2nd dose **n (%)**	1 month after 3rd dose **n (%)**	6 months after 1st dose **n (%)**
R21/Matrix-M™ + DHA-PIP + SLD-PQ				
R21/Matrix-M™				
No vaccine				

AVIDITY

Avidity -Proportion in study group with >4-fold rise from baseline to: One month after first dose; One month after second dose; One month after the third dose; Six months after the first dose for all the three groups. These will be summarised in tables 2bi to 2bii as follows:

Table 3bi. *Plasmodium falciparum*. Circumsporozoide Protein.(NANP)6 Ab.IgG Avidity

ARM	1 month after 1st dose **n (%)**	1 month after 2nd dose **n (%)**	1 month after 3rd dose **n (%)**	6 months after 1st dose **n (%)**
R21/Matrix-M™ + DHA-PIP + SLD-PQ				
R21/Matrix-M™				
No vaccine				

Table 3bii. *Plasmodium falciparum*. anti-C-Term Circumsporozoide Ab.IgG avidity

ARM	1 month after 1st dose **n (%)**	1 month after 2nd dose **n (%)**	1 month after 3rd dose **n (%)**	6 months after 1st dose **n (%)**
R21/Matrix-M™ + DHA-PIP + SLD-PQ				
R21/Matrix-M™				
No vaccine				

Table 3biii. *P falciparum*. anti-full length CSP Ab.IgG avidity

ARM	1 month after 1st dose **n (%)**	1 month after 2nd dose **n (%)**	1 month after 3rd dose **n (%)**	6 months after 1st dose **n (%)**
R21/Matrix-M™ + DHA-PIP + SLD-PQ				
R21/Matrix-M™				
No vaccine				

The frequency and the proportions of participants who are seropositive* for antibodies at each timepoint will be summarized in the table below

Table 3ci. Proportion seropositive* for antibodies at each timepoint: *Plasmodium falciparum*. Circumsporozoite Protein.(NANP)6 Ab.IgG

ARM	1 month after 1st dose **n (%)**	1 month after 2nd dose **n (%)**	1 month after 3rd dose **n (%)**	6 months after 1st dose **n (%)**
R21/Matrix-M™ + DHA-PIP + SLD-PQ				
R21/Matrix-M™				
No vaccine				

** The percentage of subjects seroconverting after each immunization based on a value greater than the mean titer at baseline (before immunization # 1) plus 2 standard deviations for all subjects included in the analysis.*

Table 3cii. Proportion seropositive* for antibodies at each timepoint: *Plasmodium falciparum*. anti-C-Term Circumsporozoide Ab.IgG

ARM	1 month after 1st dose **n (%)**	1 month after 2nd dose **n (%)**	1 month after 3rd dose **n (%)**	6 months after 1st dose **n (%)**
R21/Matrix-M™ + DHA-PIP + SLD-PQ				
R21/Matrix-M™				
No vaccine				

** The percentage of subjects seroconverting after each immunization based on a value greater than the mean titer at baseline (before immunization # 1) plus 2 standard deviations for all subjects included in the analysis.*

Table 3ciii. Proportion seropositive* for antibodies at each timepoint: *Plasmodium falciparum*. Circumsporozoite Full length (N+C-Terminal)

ARM	1 month after 1st dose **n (%)**	1 month after 2nd dose **n (%)**	1 month after 3rd dose **n (%)**	6 months after 1st dose **n (%)**
R21/Matrix-M™ + DHA-PIP + SLD-PQ				
R21/Matrix-M™				
No vaccine				

** The percentage of subjects seroconverting after each immunization based on a value greater than the mean titer at baseline (before immunization # 1) plus 2 standard deviations for all subjects included in the analysis.*

The serum anti-CS antibody titre

The serum anti-CS antibody titre -The geometric mean-in titre from baseline to: One month after first dose; One month after second dose; One month after the third dose; Six months after the first dose for all groups.

Table 4ai. *Plasmodium falciparum*. Circumsporozoite Protein.(NANP)6 Ab.IgG

ARM	1 month after 1st dose Geometric Mean (95 % CI)	1 month after 2nd dose Geometric Mean (95 % CI)	1 month after 3rd dose Geometric Mean (95 % CI)	6 months after 1st dose Geometric Mean (95 % CI)
R21/Matrix-M™ +DHA-PIP + SLD-PQ				
R21/Matrix-M™				
No vaccine				

Table 4aii. *Plasmodium falciparum*. anti-C-Term Circumsporozoide Ab.IgG

ARM	1 month after 1st dose Geometric Mean (95 % CI)	1 month after 2nd dose Geometric Mean (95 % CI)	1 monthafter 3rd dose Geometric Mean (95 % CI)	6 months after 1st dose Geometric Mean (95 % CI)
R21/Matrix-M™ + DHA-PIP + SLD-PQ				
R21/Matrix-M™				
No vaccine				

Table 4aiii. *Plasmodium falciparum*. Circumsporozoite Full length (N+C-Terminal)

ARM	1 month after 1st dose Geometric Mean (95 % CI)	1 month after 2nd dose Geometric Mean (95 % CI)	1 month after 3rd dose Geometric Mean (95 % CI)	6 months after 1st dose Geometric Mean (95 % CI)
R21/Matrix-M™ + DHA-PIP + SLD-PQ				
R21/Matrix-M™				
No vaccine				

AVIDITY (Geometric means)

Avidity -The geometric mean in titre from baseline to: One month after first dose; One month after second dose; One month after the third dose; Six months after the first dose for all groups.

Table 4bi. *Plasmodium falciparum*. Circumsporozoide Protein.(NANP)6 Ab.IgG Avidity

ARM	1 month after 1st dose Geometric Mean (95 % CI)	1 month after 1st dose Geometric Mean (95 % CI)	1 month after 3rd dose Geometric Mean (95 % CI)	6 months after 1st dose Geometric Mean (95 % CI)
R21/Matrix-M™ + DHA-PIP + SLD-PQ				
R21/Matrix-M™				
No vaccine				

Table 4bii. *Plasmodium falciparum*. anti-C-Term Circumsporozoide Ab.IgG avidity

ARM	1 month after 1st dose Geometric Mean (95 % CI)	1 month after 2nd dose Geometric Mean (95 % CI)	1 month after 3rd dose Geometric Mean (95 % CI)	6 months after 1st dose Geometric Mean (95 % CI)
R21/Matrix-M™ + DHA-PIP + SLD-PQ				
R21/Matrix-M™				
No vaccine				

Table 4biii. *P falciparum*. anti-full length CSP Ab.IgG avidity

ARM	1 month after 1st dose Geometric Mean (95 % CI)	1 month after 2nd dose Geometric Mean (95 % CI)	1 month after 3rd dose Geometric Mean (95 % CI)	6 months after 1st dose Geometric Mean (95 % CI)
R21/Matrix-M™ + DHA-PIP + SLD-PQ				
R21/Matrix-M™				
No vaccine				

5. STATISTICAL ANALYSES OF PRIMARY SAFETY ENDPOINTS

Safety analysis will be performed on patients allocated to receive vaccination. The percentage of subjects with at least one local AEs with at least one general AE (solicited and unsolicited) and with any AE during the 7-day or total follow-up period up to 28 days after the last vaccine dose and overall will be tabulated with exact 95% CI. The percentage of doses followed by at least one local AE (solicited and unsolicited), by at least one general AE (solicited and unsolicited) and by any AE during the 7-day or the total follow up period up to 28 days after the last vaccine will be tabulated with exact 95% CI. The same computations will be done for Grade 3 AEs, for any AEs considered related to vaccination and for any Grade 3 AEs considered related to vaccination. The percentage of subjects reporting each individual solicited local AE (any grade and Grade 3) and solicited general AE (any grade, Grade 3, any related, Grade 3 related, resulting in medically attended visit) during the 7-day follow-up period (Day 0-6) after each vaccine dose and overall will be tabulated for each group. Similarly, the percentage of doses followed by each individual solicited local and general AE will be tabulated, overall vaccination course, with exact 95% CI. For fever, the number and percentage of subjects reporting fever by half degree (°C) cumulative increments during the first seven days (Day 0-6) after each vaccine dose and overall will be tabulated. Similar tabulations will be performed for any fever with a causal relationship to vaccination and Grade 3 (> 39.5°C) causally related fever. The percentage of subjects reporting unsolicited AEs from the date of the first vaccine dose up to 28 days after the last vaccine dose will be tabulated by group and by MedDRA preferred term with exact 95% CI. Similar tabulation will be done for Grade 3 unsolicited AEs, for any causally related unsolicited AEs and for Grade 3 causally related unsolicited AEs. The percentage of subjects reporting SAEs and pregnancies will be described in detail. The percentage of vaccinated subjects reporting AEs of specific interest (meningitis and pIMDs) will be described in detail.

Thus, in summary, the safety analysis will be as follows:

- Frequency (%) of occurrence of solicited local and general AEs within seven days (day of vaccination and six subsequent days) after each vaccination with exact 95% CI by group and severity.
- Frequency (%) of occurrence of unsolicited AEs from the date of the first vaccination to 28 days after the last vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification with exact 95% CI, by group and severity.
- Frequency (%) of occurrence of SAEs (all, fatal, related to investigational vaccine) within 28 days (day of vaccination and 28 subsequent days) after each vaccination, according to the MedDRA classification with 95% CI.
- Frequency (%) of occurrence of SAEs (all, fatal, related to investigational vaccine) during the whole study period according to the MedDRA classification with exact 95% CI.
- Frequency (%) of occurrence of AEs and SAEs leading to withdrawal from further vaccination from Dose 1 (Day 0) up to study conclusion (Day 180), according to the MedDRA classification, for each vaccinated subject exact 95% CI.
- Frequency (%) of occurrence of pIMDs from Dose 1 (Day 0) up to study conclusion (Day 180), according to MedDRA classification, for each vaccinated subject with exact 95% CI.
- Frequency (%) of occurrence of meningitis from Dose 1 (Day 0) up to study conclusion (Day 180), according to the MedDRA classification, for each vaccinated subject exact 95% CI.

These will be summarised in table 4 below:

Table 4 Safety analysis

Safety parameter	R21/Matrix-M™ + DHA-PIP + SLD-PQ **n=X**	R21/Matrix-M™ **n=X**	**No Vaccine n=X**
Solicited local and general AEs within seven days n(%), (95% CI)			
Unsolicited AEs: date of 1st vaccine to 28 days after last vaccine n(%), (95% CI)			
SAEs within 30 days after each vaccine n (%), (95% CI)			
SAEs for whole period n (%), (95% CI)			
AEs+SAEs leading to withdrawal from further vaccination from Dose 1 to study conclusion n(%), (95% CI)			
pIMDs from Dose 1 to study conclusion n(%), (95% CI)			

Biochemistry and haematological safety assessment.

Biochemistry (ALT, AST and creatinine) and haematological (haemoglobin, WBC, and platelets) laboratory values will be presented according to toxicity grading scales and tabulated by group. The normal ranges and toxicity grading for laboratory safety parameters those will be used in this study are in Appendix section (Table A1):

The following definitions will be used for clinical adverse events in this report: The intensity should be assigned to one of the following categories:

1 (mild) = An AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

2 (moderate) = An AE which is sufficiently discomforting to interfere with normal everyday activities.

3 (severe) = An AE which prevents normal, everyday activities. In adults, such an AE would, for example, prevent attendance at work/school and would necessitate the administration of corrective therapy.

An AE that is assessed as Grade 3 (severe) will not be confused with a SAE. Grade 3 is a category used for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 3. A grade 3 AE may not necessarily be an SAE in this study.

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