CLINICAL TRIAL PROTOCOL

A non-randomized, open label, controlled, dose-escalation, phase I clinical trial to evaluate the safety, reactogenicity and immunogenicity of one or two administrations of candidate rabies mRNA vaccine CV7202 in healthy adult subjects

Protocol Number:	CV-7202-104
EudraCT Number:	2017-002856-10
Investigational medicinal product:	CV7202
Phase:	Phase I
Sponsor:	CureVac AG Schumannstr. 27 D-60325 Frankfurt Germany
Short Title:	Safety, reactogenicity and immunogenicity of CV7202 in healthy adult subjects
Protocol Date:	30 April 2020
Protocol Version:	2.0
Version History	N/A

APPROVAL SIGNATURES

Protocol Title: A non-randomized, open label, controlled, dose-escalation, phase I clinical trial to evaluate the safety, reactogenicity and immunogenicity of one or two administrations of candidate rabies mRNA vaccine CV7202 in healthy adult subjects

Protocol Number: CV-7202-104

This trial will be conducted with the highest respect for the individual subjects in compliance with the requirements of this clinical trial protocol (and amendments), and also in compliance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 (R2) Good Clinical Practice (GCP): Revised and consolidated guidelines [1].
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

Sponsor Signatory

[redacted]

Signature

Date

[redacted]

SAE Hotline	
SAE reporting to [redacted] **by fax or email within 24 hours** after discovery:	
Europe	[redacted]
SAE Fax-no.:	
Email:	
Address:	

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1 Synopsis

Protocol Title:	A non-randomized, open label, controlled, dose-escalation, phase I clinical trial to evaluate the safety, reactogenicity and immunogenicity of one or two administrations of candidate rabies mRNA vaccine CV7202 in healthy adult subjects
Short Title:	Safety, reactogenicity and immunogenicity of CV7202 in healthy adult subjects
Rationale:	The objectives of this phase I trial are to assess the safety and reactogenicity of CV7202 in the context of immune responses to rabies virus glycoprotein (RABV-G) in order to select the optimal dose and number of doses. The dose range selected is intended to provide data for defining the optimal dosage of CV7202 to be tested in subsequent clinical trials.
Sponsor:	CureVac AG Schumannstr. 27 D-60325 Frankfurt Germany
Coordinating/ Principal Investigator:	[redacted]

Trial Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To assess the safety and reactogenicity profile of CV7202 administered intramuscularly (i.m.) to healthy adults (18–40 years old), as a range of doses (1, 2 and 5 µg) in one- or two-dose regimens.	• The percentages of subjects with, and the frequencies and intensities of solicited local adverse events (AEs) reported on the day of vaccination and the 7 subsequent days (Days 1-8).
	• The percentages of subjects with, and the frequencies, intensities and relationship to vaccination, of solicited systemic AEs reported on the day of vaccination and the 7 subsequent days (Days 1-8).
	• The duration (in days) of solicited local AEs, of solicited systemic AEs and of the individual solicited AEs.

	• The percentages of subjects with and frequencies and intensities of any unsolicited and related unsolicited AEs reported on the day of vaccination and the 28 subsequent days (Days 1-29).
	• The percentages of subjects with and frequencies and relationship to vaccination of any serious adverse events (SAEs) and any medically-attended AEs (MAAEs) up to 12 months post last dose.
	• The percentages of subjects with and frequencies and relationship to vaccination of any adverse events of special interest (AESIs) up to 12 months post vaccination.
Secondary	
For safety:	
• To assess the safety profile of CV7202 administered i.m. to healthy adults (18-40 years old), as a range of doses (1, 2 and 5 µg) in one- or two-dose regimens in the period from 12 to 24 months post last dose.	• The percentages of subjects with and frequencies of SAEs and MAAEs related to study vaccination from 12 months post last dose up to 24 months post last dose (trial end).
	• The percentages of subjects with and frequencies and relationship to vaccination of any AESIs from 12 months post last dose up to 24 months post last dose (trial end).
For the characterization of the humoral immune response:	
• To evaluate the potential protective immune responses to CV7202 and Rabipur® in healthy adults (18–40 years old), by assessing the percentages of subjects with rabies-specific serum virus-neutralizing antibody titers (VNTs) ≥0.5 IU/ml.	• Percentages of subjects with rabies-specific serum VNTs ≥0.5 IU/ml by trial group on Days 1 (pre-vaccination), 15, 43, and 12, 18* and 24* months post last dose. * Will be performed only in subjects with detectable RABV-G-specific IgG at 6 months after the last vaccination or Day 91 if the Month 6 blood sample is not available.

• To evaluate the immunogenicity (VNTs) of CV7202 administered to healthy adults (18–40 years old), as a range of doses (1, 2 and 5 µg) in one- or two-dose regimens and the immunogenicity of Rabipur® administered in a 3-dose regimen.	• Serum geometric mean titers (GMTs) of virus-neutralizing antibodies by trial group on Days 1, 8, 15, 29, 36, 43, 57, 91, and 6, 12, 18* and 24* months post-last dose. * Will be performed only in subjects with detectable RABV-G-specific IgG at 6 months after the last vaccination or Day 91 if the Month 6 blood sample is not available.
Exploratory	
For the evaluation of the innate immune response:	
• To evaluate the innate immune response to one or two doses of CV7202 compared with baseline.	• Serum cytokine concentrations*, including but not limited to CXCL10, CCL3, IL-6, TNF-α and IFN-γ, at pre-vaccination and 4 hours post-vaccination on Day 1, and Days 2 or 3** and 8 after each vaccination.
	• Transcriptome profiling* on the day of vaccination at pre-vaccination, and Days 2 or 3** and 8 after each vaccination. * Will be performed in the first 5 subjects in Group 2 (** on Day 3) and all subjects in Groups 3 and 4 (** on Day 2). Note that Day 3 was planned in the original protocol and only applies to subjects in Group 2 who were already enrolled and vaccinated before this protocol amendment was issued. Day 2 applies to all other subjects.
For the evaluation of antigen specific T-cell response:	
• To evaluate the frequencies and functionalities of RABV-G-specific T cells after one or two doses of CV7202 compared with baseline.	• The frequencies and functionalities of RABV-G-specific T cells in peripheral blood from the first 5 subjects in Group 2 and all subjects in Groups 3 and 4 on Days 1, 8, 36, 91*, and 6* and 12* months post-last dose. * For groups that have shown a significant T-cell response at Day 8 or 36 compared to baseline.
For the evaluation and characterization of the B-cell response:	
• To evaluate the frequencies of RABV-G-specific B cells after one or two doses of CV7202 compared with baseline.	• The frequencies of RABV-G-specific B cells in peripheral blood from the first 5 subjects in Group 2 and all subjects in Groups 3 and 4 on Days 1, 8, 36, 91*, and 6* and 12* months post-last dose.

• To evaluate the effect of vaccination on B-cell phenotype and activation after one or two doses of CV7202 compared with baseline.	• The frequencies and activation status of phenotypically distinct subsets of B cell populations, including but not limited to naïve and memory B cells, plasmablasts and plasma cells for the first 5 subjects in Group 2 and all subjects in Groups 3 and 4 on Days 1, 8, 36, 91*, and 6* and 12* months post-last dose.
• To evaluate the effect of vaccination on B-cell clonality after one or two doses of CV7202 compared with baseline.	• Sequencing of B-cell receptors (BCR) of circulating B cells on Days 1, 8, 29, 36, 57, 91*, and 6* and 12* months post-last dose. * For groups that have shown a significant B-cell response at Day 8 or 36 compared to baseline.
For the characterization of the humoral immune response:	
• To evaluate RABV-G-specific antibody responses throughout the trial including the follow-up period by assessing IgM, IgG and IgA levels.	• RABV-G-specific IgM, IgG and IgA levels measured by ELISA on Days 1, 8, 15, 29, 36, 43, 57, 91, and 6 and 12 months post-last dose. • RABV-G-specific IgG levels measured by ELISA 18* and 24* months post-last dose. * Will be performed only in subjects with detectable RABV-G-specific IgG at 6 months after the last vaccination or Day 91 if the Month 6 blood sample is not available.
• To characterize the nature and quality of the RABV-G-specific antibody response, by measuring the serum affinity and avidity after one or two doses of CV7202 and the breadth of neutralization against heterologous lyssaviruses with variant epitopes.	• Identification of epitopes recognized by vaccine-induced antibodies on Days 1, 15, 43, and 12 months post last dose*. • Measurement of RABV-G-specific antibody avidity and affinity on Days 1, 15, 43, and 12 months post last dose*. • Measurement of VNTs against additional heterologous lyssaviruses on Days 1, 15, 43, and 12 months post last dose*. * Will be performed only on selected samples with VNT >0.5 IU/ml.
Overall Design:	This is a non-randomized, open label, controlled, dose-escalation, phase I clinical trial to evaluate the safety, reactogenicity and immunogenicity of one or two i.m. administrations of candidate rabies mRNA vaccine CV7202 in healthy adult subjects. The subjects will be enrolled sequentially in up to 4 trial groups to receive either a dose of CV7202 containing different mRNA content or Rabipur®. In a first CV7202 group, 10 subjects have received a dose containing 5 µg mRNA. A dose of 1 or 2 µg mRNA will be administered to 2 additional

<table>
<tr><td></td><td>groups of 16 subjects each, of whom 8 in each group will be administered a second dose 28 days later.

A control group of 10 subjects will receive 3 doses of the licensed vaccine Rabipur® according to the manufacturer's recommendations. Safety and immunogenicity assessments will be made up to 2 years following the last dose administration. Specified safety data will be reviewed by an internal safety review committee (iSRC) and a data safety monitoring board (DSMB) on a pre-defined schedule.</td></tr>
<tr><td>Trial Population Key Inclusion Criteria:</td><td>1. Healthy male and female subjects aged 18 to 40 years inclusive.
2. Expected to be compliant with protocol procedures and available for clinical follow-up through the last planned visit.
3. Physical examination and laboratory results without clinically significant findings.

The full list of inclusion criteria is provided in the protocol.</td></tr>
<tr><td>Trial Population Key Exclusion Criteria:</td><td>1. Receipt of licensed or investigational rabies vaccine prior to the administration of the trial vaccine.
2. History of potential immune mediated disease.
3. Known allergy to any component of CV7202 or Rabipur®.

The full list of exclusion criteria is provided in the protocol.</td></tr>
<tr><td>Number of Subjects:</td><td>Approximately 52 subjects will be enrolled.</td></tr>
<tr><td>Vaccination Groups and Duration:</td><td>
<table>
<tr><th></th><th rowspan="2">Trial Product</th><th rowspan="2">Composition</th><th colspan="3">Dosing</th></tr>
<tr><th>Day 1</th><th>Day 8</th><th>Day 29</th></tr>
<tr><th></th><th></th><th></th><th>N</th><th>N</th><th>N</th></tr>
<tr><td>Group 1</td><td>Rabipur®</td><td>N/A</td><td>10</td><td>10</td><td>10</td></tr>
<tr><td>Group 2*</td><td rowspan="4">CV7202</td><td>5 µg mRNA</td><td>10</td><td rowspan="4">NA</td><td>N/A</td></tr>
<tr><td>Group 3
• Group 3a**</td><td>1 µg mRNA</td><td>16</td><td>8</td></tr>
<tr><td>Group 4
• Group 4a**</td><td>2 µg mRNA</td><td>16</td><td>8</td></tr>
<tr><td>Total CV7202</td><td></td><td></td><td>42</td><td></td><td>16</td></tr>
</table>
* Note that enrolment in Group 2 was already completed at the time this protocol amendment was issued.
** 'a' groups are a subset consisting of 8 subjects of Groups 3 and 4 scheduled to receive a first dose on Day 1 and a second dose on Day 29.</td></tr>
<tr><td>Measurements and Assessments:</td><td>Due to the exploratory nature of this trial only descriptive statistics will be used, no confirmatory statistical inference will be performed.

Safety set: This is the subset of subjects, who have received at least one dose of the candidate rabies mRNA vaccine CV7202 or the active control Rabipur® and for whom any post-Day 1 safety data are available. The analysis of safety will be performed on this population.

Full-analysis (FA) set: This is the subset of the Safety Set with subjects who have the baseline sample and at least one additional blood sample available for VNT analysis. This analysis set is the primary analysis set for all immunogenicity objectives.</td></tr>
</table>

	Primary and secondary safety and reactogenicity will be assessed as follows: 1. AEs (type, intensity, frequency and relationship to vaccination), i.e. incidence and severity of AEs for both solicited local and systemic events (reported on the day of vaccination and the 7 subsequent days [Days 1-8]) and unsolicited events (reported on the day of vaccination and the 28 subsequent days [Days 1-29]). 2. SAEs, MAAEs and AEs leading to trial or vaccine withdrawal up to 12 months post last dose. After Visit 15 (Month 12), only SAEs and MAAEs that according to the investigator are considered to be related to study vaccination will be collected. 3. Intercurrent medical conditions and AESIs throughout the trial. 4. Local reactogenicity assessment of injection site in all subjects. Further safety assessments will be conducted based on vital signs and laboratory assessments. Results will be summarized in tables and supported by subject level listings. Secondary immunogenicity endpoints: 1. Number and percentage of subjects having VNTs ≥0.5 IU/ml on Days 1, 15, 43, and 12, 18 and 24 months post last dose. 2. Individual functional antibody titers, GMTs and range of titers in sera collected on Days 1, 8, 15, 29, 36, 43, 57, and 12, 18 and 24 months post last dose. Further immunogenicity assessments will be based on VNTs, RABV-G-specific immunoglobulins (Ig) IgG, IgM and IgA serum antibodies and other immunogenicity-related parameters throughout the duration of the trial. Results will be summarized in tables, figures and supported by subject level listings. No statistically-based sample size estimation was performed.

2 Schedule of Activities

Table 2.1 Schedule of Activities

Visit Type		Pre-screening	Screening	Clinic visit		Phone call	Clinic visit					Phone call	Clinic visit				Clinic visit/***							
Trial Day		**-90 to -1***	**-30 to -1***	**1**	**2†**	**3**	**8**	**10**	**15**	**29**	**30#†**	**31**	**36**	**43**	**57**	**91**	**M6**		**M12**		**M18**		**M24**	
Visit Window (days)		N/A	N/A	N/A	+/- 2**	-	+1	-1/+2	-1/+2	+/- 2	+/- 2**	-	-1/+2	+/- 2	+/- 2	+/- 7	+/- 14	+ 15-90	+/- 30	+ 31-90	+/- 30	+ 31-90	+/- 30	+31-180
Visit Number		1	2	3	4	-	5	6	7	8	9	-	10	11	12	13	14	14A	15	15A	16	16A	17	17A
Procedure	**References**					CV7202 groups only		Group 1 only			Groups 1, 3a and 4a only	CV7202 groups only												
Signed Informed Consent [a]	9.4.1	X																						
Medical History	9.4.1	X																						
Inclusion/Exclusion criteria	6.1, 6.2, 9.4.1, 9.4.2, 9.4.3	X	X	X																				
Vaccine delay recommendations	6.3, 9.4.3, 9.4.6, 9.4.9			X			X			X#														
Demographics	9.4.1	X																						
Pregnancy Test	9.4.2, 9.4.3, 9.4.6, 9.4.9		X [b]	X [c]			X [c]			X# [c]														
Vaccination																								
CV7202	9.4.3, 9.4.9			X						X [d]														
Rabipur®	9.4.3, 9.4.6, 9.4.9			X			X			X														
Safety monitoring																								
Physical Examination [e]	9.4.2-9.4.11, 9.4.14, 9.4.15, 9.4.17, 0		X	X	X		X	X	X	X	X		X		X	X			X	X			X	X
12-lead Electrocardiogram	9.4.2		X																					
Vital signs [f]	9.4.1, 9.4.3-9.4.11, 9.4.17, 0	X		X	X		X	X	X	X#	X		X						X	X			X	X
Post-injection vaccination site reactogenicity assessment [g]	9.4.3-9.4.7, 9.4.9-9.4.10			X	X		X	X		X#	X													
Diary dispensed/training [h]	9.4.3, 9.4.5, 9.4.9			X			X			X#														
Diary review/reminder [h]	9.4.4-9.4.14				X		X	X	X	X	X		X	X	X									
Diary collection [h]	9.4.5, 9.4.9, 9.4.14						X			X					X									
Assess all post-dose solicited AEs	9.4.3-9.4.12			X	X	X	X	X	X	X#	X	X	X											
Assess all post-dose unsolicited AEs	9.4.3-9.4.14			X	X	X	X	X	X	X#	X	X	X	X	X									
Assess all SAEs	9.4.3-9.4.17	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Assess all MAAEs	9.4.3-9.4.17	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Assess AEs leading to premature withdrawal	9.4.3-9.4.17	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Assess intercurrent medical conditions	9.4.3-0	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess Concomitant Medications/Vaccinations	9.4.2-0		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess AESIs	9.4.3-0	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess SAEs related to study vaccination [m]	9.4.3-0																				X	X	X	X
Assess MAAEs related to study vaccination [m]	9.4.3-0																				X	X	X	X
Safety Lab [i] (~9 ml)	9.4.2-9.4.5, 9.4.8-9.4.11, 9.4.14-9.4.17		X [j,k]	X [j,k]	X [j,k]		X [j]		X [j]	X [j]	X [j,k]		X [j]		X [j]	X [j]	X [j]	X [j]	X [j]	X [j]			X [o]	X [o]
TSH, Thyroid antibodies, ANA (~3 ml)§	9.5.2	X																						
Immunogenicity																								
VNTs (serum) [i] (~18ml)	9.4.3, 9.4.5, 9.4.8, 9.4.9, 9.4.11-0			X			X		X	X			X	X	X	X	X	X	X	X	X [n]	X [n]	X [n]	X [n]
IgM/ IgG/ IgA ELISA (serum) [i] (~6 ml)	9.4.3, 9.4.5, 9.4.8, 9.4.9, 9.4.11-0			X			X		X	X			X	X	X	X	X	X	X	X	X [n]	X [n]	X [n]	X [n]
Cellular immune response and leukocyte phenotyping (PBMCs) [i,l] (~40-60 ml)	9.4.3, 9.4.5, 9.4.11, 9.4.15-9.4.17			X			X						X			X	X	X	X	X				
Cytokine assessment (serum) [i,l] (~6 ml)	9.4.3-9.4.5, 9.4.9-9.4.11			X‡	X		X			X#, ‡	X		X											
Transcriptome profiling (PBMCs) [i,l] (~10ml)	9.4.3, 9.4.4, 9.4.9, 9.4.10			X	X		X			X#	X		X											
Immune receptor sequencing (PAXgene DNA) [i] (~5ml)	9.4.3, 9.4.5, 9.4.9, 9.4.11, 9.4.14-9.4.17			X			X			X			X		X	X	X	X	X	X				
Maximum total blood volume (ml)	Table 9.3	3	11	120	25	0	94	0	33	60	25	0	94	24	38	78	78	78	78	78	24	24	24	24
Trial end																								X

Notes:

M6 corresponds to Day 181 (1-dose groups) and Day 209 [2-dose groups and Group 1 (Rabipur®)].

M12 corresponds to Day 365 (1-dose groups) and Day 393 [2-dose groups and Group 1 (Rabipur®)].

M18 corresponds to Day 547 (all groups).

M24 corresponds to Day 729 (all groups).

Vaccinations planned at Visit 3 (Dose 1 for Groups 1 to 4), Visit 5 (Dose 2 Rabipur® for Group 1), Visit 8 (Dose 2 for Groups 3a and 4a, Dose 3 Rabipur® for Group 1).

* The pre-screening and screening visits can be performed on the same day.

** The Day 2 and Day 30 visits should be performed at around 24 +/- 2 hours after the vaccination.

† Note that for subjects in Groups 1 and 2, who were already enrolled and vaccinated before Protocol Amendment 1 was issued, Visit 4 occurred on Day 3 and Visit 9 occurred on Day 31 as planned in the original protocol.

§ Blood drawn at the pre-screening visit will be kept for retrospective measurement of TSH, thyroid antibodies and ANA following the occurrence of clinical autoimmune events (other autoantibodies might be investigated as well depending on the

clinical autoimmune event).

=Only for subjects receiving vaccination (Dose 2 for Groups 3a and 4a, Dose 3 Rabipur® for Group 1)

‡ Two blood samples for cytokine assessment will be drawn on the days of vaccination, including one pre-vaccination sample and one sample at 4 hours post-vaccination (Only for CV7202 groups).

*** The optional Visits 14A, 15A, 16A and 17A should only take place in case the respective visit could not be conducted as described in the protocol. In case Visit 14, 15, 16 or 17 cannot take place on site due to the public health emergency related to COVID-19, safety information should be collected via a phone call within the protocol-allowed time interval for the respective visit. However, if the investigator judges that the benefits of a site visit outweigh the risks based on clinical symptoms, the visit should take place on site. In this case, all procedures as indicated in this table for the respective time point should be performed, if possible. If the information was collected via a phone call, the respective Visit A should be scheduled on site within the protocol-allowed time interval and all indicated procedures, including blood sampling, should be performed. Also, in case the visit was conducted on site but not all procedures could be performed, the respective Visit A should be scheduled on site within the protocol-allowed time interval.

Abbreviations: AE=Adverse event; AESI = Adverse event of special interest; ANA = Antinuclear antibody; ELISA = Enzyme-linked immunosorbent assay; Ig = Immunoglobulin; MAAE = Medically-attended adverse event; PBMC = Peripheral blood mononuclear cell: SAE = Serious adverse event; TSH = Thyroid-stimulating hormone; VNT = Virus-neutralizing antibody titers;

[a] Informed consent form(s) signed prior to any procedures.

[b] In women of childbearing potential, serum pregnancy test. A 3 ml blood sample will be taken.

[c] In women of childbearing potential, urine pregnancy tests will be performed before each vaccination, unless the serum pregnancy test was performed less than 3 days before.

[d] Second vaccination of CV7202 will be given only to 8 subjects in Groups 3 and 4 (i.e. Groups 3a and 4a).

[e] Physical examination and vital signs must be performed/analyzed by a qualified healthcare professional.

[f] Vital signs to be checked: body temperature, pulse, blood pressure. Vital signs will be measured pre- and post-vaccination prior to discharge. Subjects will be observed for 4 hours following each vaccination; vital signs must be within normal or clinically non -relevant abnormal ranges or have returned to pre-vaccination values for the subject to be discharged from the phase I Unit.

[g] All vaccinated subjects will undergo vaccination site reactogenicity assessment at 1 hour post-vaccination on the day of vaccination (Day 1, Day 8 and Day 29) and 1 or 2 days after each vaccination (Day 2 or 3, Day 10 and Day 30 or 31). Note that Days 3 and 31 were planned in the original protocol and only apply to subjects in Groups 1 and 2 who were already enrolled and vaccinated before this protocol amendment was issued. Local reactions (injection site pain, redness, swelling and itching) will be assessed on an intensity scale of absent, mild, moderate and severe.

[h] Solicited and unsolicited AE diaries. Solicited AEs occurring on the day of vaccination (Day 1, Day 8 and Day 29) and for the following 7 days will be recorded by the subject on the diary card. The diary card will be reviewed on Day 2 or 3, 8, 10, 15 29, 30 or 31, 36, 43 and 57. Unsolicited AEs occurring on the day of vaccination (Day 1, Day 8 and Day 29) and for the following 28 days will be recorded by the subject on the diary card.

[i] The VNT serum sample is intended as the baseline value and must be taken before vaccination on Day 1 and Day 29.

[j] Hematology (complete blood count, including differential and platelets), biochemistry.

[k] Coagulation (activated partial thromboplastin time [aPTT]) and prothrombin time/international normalized ratio (INR) will be performed at the following time points: Screening, Day 1, Day 2 or 3 and Day 30 or 31.

[l] In the first 5 subjects in Group 2 and all subjects in Groups 3 and 4. 60 ml for the baseline (Day 1) time point, 40 ml for subsequent blood draws.

[m] At each study visit/contact preceding Month 18, SAE and MAAEs considered as related to study vaccination were collected as part of all SAEs and MAAEs.

[n] At Month 18 and Month 24, VNTs and IgG assessments will be performed only in subjects with detectable RABV-G-specific IgG at 6 months after the last vaccination or Day 91 if the Month 6 blood sample is not available.

[o] If no blood sampling could be performed at Visit 15 and the optional Visit 15A, the end-of-trial blood sample for safety assessment may be performed at Visit 17 (Month 24).

Table 2.2 Staggered Enrolment and Dose Escalation for Groups 2 to 4 (Dose 1) with Minimum Time Intervals*

Week#*	Group #2		Groups #3 - #4	
	Dose 1 (Day 1)	**Review**	**Dose 1 (Day 1)**	**Review**
1	#1 (enrol) Day 1			
	#2 - #3 Day 3			
2	#4 - #5 Day 1	iSRC**		
3	#6 - #10 (enrol)			
7		DSMB **GO/NO GO (next dose level)**		
8			#1 (enrol) Day 1	
			#2 Day 3	
9			#3 - #4 Day 1	iSRC**
10 -11			#5 - #16 (enrol)§	
12				DSMB **GO/NO GO (next dose level)**
13 – 42			**Enrolment cycle for Group 4†**	

DSMB (Data safety monitoring board) provides recommendation to proceed or not with dose-escalation; iSRC = Internal safety review committee; Day 1 corresponds to Monday, Day 3 corresponds to Wednesday.
* These intervals may be prolonged at the discretion of the investigator or upon request of the sponsor or DSMB for safety or operational reasons;
** The iSRC will take place only once the last subject in the sentinel group (first 5 subjects of Group 2, first 4 subjects in Groups 3 and 4 and subsequent 6 subjects in Groups 3 and 4) has been vaccinated and followed up for at least 2 working days.
§ The staggered enrolment for the initial 4 subjects may be extended to the subsequent subjects in Groups 3 or 4. The number of subjects in this extended staggered enrolment may be further established by the investigator, sponsor or DSMB based on the data obtained in earlier enrolled subjects in these groups.
† Enrolment in Group 4 can proceed as for Group 3 with a duration of a minimum of 7 weeks. A slower enrolment schedule can be followed in agreement with the investigator and sponsor, if needed with input from the iSRC or DSMB.

3 Introduction

Rabies is a viral zoonosis which causes acute encephalitis in mammals including humans. The disease is virtually always fatal once clinical symptoms develop. There are an estimated 59 000 rabies-related deaths each year [2]. The virus is endemic worldwide, but human mortality due to rabies differs markedly from continent to continent [3]. Recognizing that rabies remains a neglected disease in Asia and Africa despite the existence of safe and effective vaccines, the World Health Organization (WHO) Strategic Advisory Group of Experts on Immunization (SAGE), established a working group on rabies vaccines and immunoglobulins (Igs) in 2016 to review scientific evidence, programmatic considerations and vaccine regimens of existing therapies, and also to evaluate the potential impact of new biologicals [4].

Existing rabies vaccines can be used for both pre-exposure and post-exposure prophylaxis. Although pre-exposure prophylaxis is primarily used by animal handlers, laboratory personnel, veterinarians and forestry workers in Europe and North America, rabies prophylaxis is also appropriate for travelers to high-risk regions [5].

The US Centers for Disease Control and Prevention (CDC) reported a range of approximately 16–200 possible exposures per 100 000 travelers [6], while a 2008 study from Thailand assessed the risk of rabies exposure among 870 backpackers and found that 3.6% of them had been licked and 0.7% had been bitten by an animal [7]. Despite the demonstrated risk of rabies exposure to travelers in high-risk regions, compliance with the three injection primary vaccination series is suboptimal. Gautret and Parola reported that 76% of travelers for whom vaccination was recommended by the travel clinic physician either declined vaccination or did not have time to complete the primary three-dose vaccination series [8]. Similarly, in canine rabies infected areas, such as countries of Southeast Asia, pre-exposure prophylaxis of children has been proposed but not implemented. Children under the age of 15 are the most frequently exposed, representing 40% of human exposures [9], and would benefit from pre-exposure prophylaxis. A study assessing pre-exposure prophylaxis against rabies among school-aged children in Bangalore, India, suggests that this approach may be a useful tool for protecting children in highly endemic regions [10].

Although safe and effective, existing vaccines have limitations: they require refrigeration, a three-injection primary series for pre-exposure prophylaxis and virus inactivation steps during manufacturing which may lead to lot failure. In recognizing the ongoing need for an effective and convenient rabies vaccine, CureVac proposes to apply its proprietary messenger ribonucleic acid (mRNA) platform to develop a shelf-stable, polygeline-free, safe and effective vaccine which can be used for both pre-exposure and post-exposure prophylaxis in humans.

3.1 RNActive® technology

During translation mRNA serves as the template for protein synthesis and mRNA-based vaccines offer the possibility to vaccinate against any infectious disease that is preventable by providing or increasing the immune response against the protein antigen. However, mRNA molecules are highly unstable under physiological conditions, limiting their therapeutic application [11]. Research into achieving ribonucleic acid (RNA) stability has led to the development of different RNA delivery systems [12], including CureVac's mRNA technology (RNActive®).

The RNActive® technology employs formulated mRNA as a vaccine vector to allow for direct translation of target protein antigens within a recipient's cells. RNActive® vaccines formulated with lipid nanoparticles (LNPs) consist of an mRNA encoding the antigen of interest, which is encapsulated by LNPs. The mRNA provides strong antigen expression. The encapsulation of mRNA in LNPs is intended to facilitate and enhance the uptake of mRNA by cells. As a result of mRNA translation, antigen presentation and immune stimulation, strong and persistent adaptive immune responses against the encoded antigens are induced in animal models [13, 14].

A phase I trial evaluating the first candidate rabies mRNA vaccine formulated with protamine (CV-7201-102) induced boostable virus-neutralizing antibodies after needle-free (intradermal [i.d.] or intramuscular [i.m.]) injection, whereas needle-based (i.d. and i.m.) injection was ineffective [15]. The vaccine appeared generally safe with an acceptable reactogenicity profile. This trial provided important guidance for advances in CureVac's mRNA technology (RNActive®) particularly with respect to development of improved vaccine candidates formulated with lipid nanoparticles (LNP), which have been demonstrated to efficiently deliver mRNA in vivo to the cytoplasm of cells, where the encoded antigens are translated into proteins able to elicit antigen-specific immune responses [16].

The new candidate rabies mRNA vaccine, CV7202, is composed of R1803 (the identical active pharmaceutical ingredient [API], used in CV-7201-102), encapsulated in the novel LNP delivery system. mRNA-based vaccines based on this new delivery system have been shown to induce substantially higher and more durable virus-neutralizing antibody titers (VNTs) compared with protamine-formulated vaccines in several animal models [13] and elicit comparable responses in NHPs to those seen with licensed vaccines [17].

The current clinical study CV-7202-104 is ongoing with 10 subjects having received CV7202 up to date and being followed-up. Therefore, only preliminary clinical safety and immunogenicity data are available at this time.

The proposed trial will assess the safety, reactogenicity and immunogenicity of different doses of CV7202 in healthy adult subjects (18–40 years of age) administered i.m. as one or two doses. The active control, Rabipur® will be administered in previously unvaccinated subjects, as the three recommended doses.

The trial will be conducted in accordance with the protocol, the ICH-GCP Guidelines [1], European Medicines Agency (EMA) guidelines for first-in-human (FIH) clinical trials [22] and applicable regulatory requirements.

Refer to the current Investigator's Brochure (IB) for CV7202 for additional product information [17].

4 Objectives and Endpoints

The primary, secondary, and exploratory objectives and endpoints of this trial are listed in sections 4.1 and 4.2.

4.1 Objectives

Primary Objective:

To assess the safety and reactogenicity profile of CV7202 administered i.m. to healthy adults (18–40 years old), as a range of doses (1, 2 and 5 µg) in one- or two-dose regimens.

Secondary Objectives:

For safety

- To assess the safety profile of CV7202 administered i.m. to healthy adults (18-40 years old), as a range of doses (1, 2 and 5 µg) in one- or two-dose regimens in the period from 12 to 24 months post last dose.

For the characterization of the humoral immune response

- To evaluate the potential protective immune responses to CV7202 and Rabipur® in healthy adults (18–40 years old), by assessing the percentages of subjects with rabies-specific serum VNTs ≥0.5 IU/ml.
- To evaluate the immunogenicity (VNTs) of CV7202 administered to healthy adults (18–40 years old), as a range of doses (1, 2 and 5 µg) in one- or two-dose regimens and the immunogenicity of Rabipur® administered in a 3-dose regimen.

Exploratory Objectives:

For the evaluation of the innate immune response

- To evaluate the innate immune response to one or two doses of CV7202 compared with baseline.

For the evaluation of antigen specific T-cell response

- To evaluate the frequencies and functionalities of rabies virus glycoprotein (RABV-G)-specific T cells after one or two doses of CV7202 compared with baseline.

For the evaluation and characterization of the B-cell response

- To evaluate the frequencies of RABV-G-specific B cells after one or two doses of CV7202 compared with baseline.
- To evaluate the effect of vaccination on B-cell phenotype and activation after one or two doses of CV7202 compared with baseline.
- To evaluate the effect of vaccination on B-cell clonality after one or two doses of CV7202 compared with baseline.

For the characterization of the humoral immune response

- To evaluate RABV-G-specific antibody responses throughout the trial including the follow-up period by assessing IgM, IgG and IgA levels.

- To characterize the nature and quality of the RABV-G-specific antibody response, by measuring the serum affinity and avidity after one or two doses of CV7202 and the breadth of neutralization against heterologous lyssaviruses with variant epitopes.

4.2 Endpoints

Primary Endpoints:

- The percentages of subjects with, and the frequencies and intensities of solicited local adverse events (AEs) reported on the day of vaccination and the 7 subsequent days (Days 1-8).
- The percentages of subjects with, and the frequencies, intensities and relationship to vaccination, of solicited systemic AEs reported on the day of vaccination and the 7 subsequent days (Days 1-8).
- The duration (in days) of solicited local AE, of solicited systemic AE and of the individual solicited AEs.
- The percentages of subjects with and frequencies and intensities of any unsolicited and related unsolicited AEs reported on the day of vaccination and the 28 subsequent days (Days 1-29).
- The percentages of subjects with and frequencies and relationship to vaccination, of any serious adverse events (SAEs) and any MAAEs up to 12 months post last dose.
- The percentages of subjects with and frequencies and relationship to vaccination of any adverse events of special interest (AESIs) up to 12 months post vaccination.

Secondary Endpoints:

For safety

- The percentages of subjects with and frequencies of SAEs and MAAEs related to study vaccination from 12 months post last dose up to 24 months post last dose (trial end).
- The percentages of subjects with and frequencies and relationship to vaccination of any AESIs from 12 months post last dose up to 24 months post last dose (trial end).

For the characterization of the humoral immune response

- Percentages of subjects with rabies-specific serum VNTs ≥0.5 IU/ml by trial group on Days 1 (pre-vaccination), 15, 43, and 12, 18* and 24* months post last dose.
- Serum geometric mean titers (GMTs) of VNTs by trial group on Days 1, 8, 15, 29, 36, 43, 57, 91, and 6 and 12, 18* and 24* months post-last dose.

* Will be performed only in subjects with detectable RABV-G-specific IgG at 6 months after the last vaccination or Day 91 if the Month 6 blood sample is not available.

Exploratory Endpoints:

For the evaluation of the innate immune response:

- Serum cytokine concentrations* including but not limited to CXCL10, CCL3, IL-6, TNF-α and IFN-γ, at pre-vaccination and 4 hours post-vaccination on Day 1, and Days 2 or 3** and 8 after each vaccination.
- Transcriptome profiling* on the day of vaccination at pre-vaccination, and Days 2 or 3** and 8 after each vaccination.

* Will be performed in the first 5 subjects in Group 2 (** on Day 3) and all subjects in Groups 3 and 4 (** on Day 2). Note that Day 3 was planned in the original protocol and only applies to subjects in Groups 1 and 2 who were already enrolled and vaccinated before this protocol amendment was issued. Day 2 applies to all other subjects.

For the evaluation of antigen specific T-cell response:

- The frequencies and functionalities of RABV-G-specific T cells in peripheral blood from the first 5 subjects in Group 2 and all subjects in Groups 3 and 4 on Days 1, 8, 36, 91*, and 6* and 12* months post-last dose.

* For groups that have shown a significant T-cell response at Day 8 or 36 compared to baseline.

For the evaluation and characterization of the B cell response

- The frequencies of RABV-G-specific B cells in peripheral blood from the first 5 subjects in Group 2 and all subjects in Groups 3 and 4 on Days 1, 8, 36, 91*, and 6* and 12* months post-last dose.
- The frequencies and activation status of phenotypically distinct subsets of B cell populations, including but not limited to naïve and memory B cells, plasmablasts and plasma cells for the first 5 subjects in Group 2 and all subjects in Groups 3 and 4 on Days 1, 8, 36, 91*, and 6* and 12* months post-last dose.
- Sequencing of B-cell receptors (BCR) of circulating B cells on Days 1, 8, 29, 36, 57, 91*, and 6* and 12* months post-last dose.

* For groups that have shown a significant B-cell response at Day 8 or 36 compared to baseline.

For the characterization of the humoral immune response:

- RABV-G-specific IgM, IgG and IgA levels measured by ELISA on Days 1, 8, 15, 29, 36, 43, 57, 91, and 6 and 12 months post-last dose.
- RABV-G-specific IgG levels measured by ELISA 18* and 24* months post-last dose.
- Identification of epitopes recognized by vaccine-induced antibodies on Days 1, 15, 43, and 2, 6 and 12 months post-last dose**.
- Measurement of RABV-G-specific antibody avidity and affinity on Days 1, 15, 43, and 2, 6 and 12 months post-last dose**.

- Measurement of VNTs against additional heterologous lyssaviruses on Days 1, 15, 43, and 2, 6 and 12 months post-last dose**.

* Will be performed only in subjects with detectable RABV-G-specific IgG at 6 months after the last vaccination or Day 91 if the Month 6 blood sample is not available.

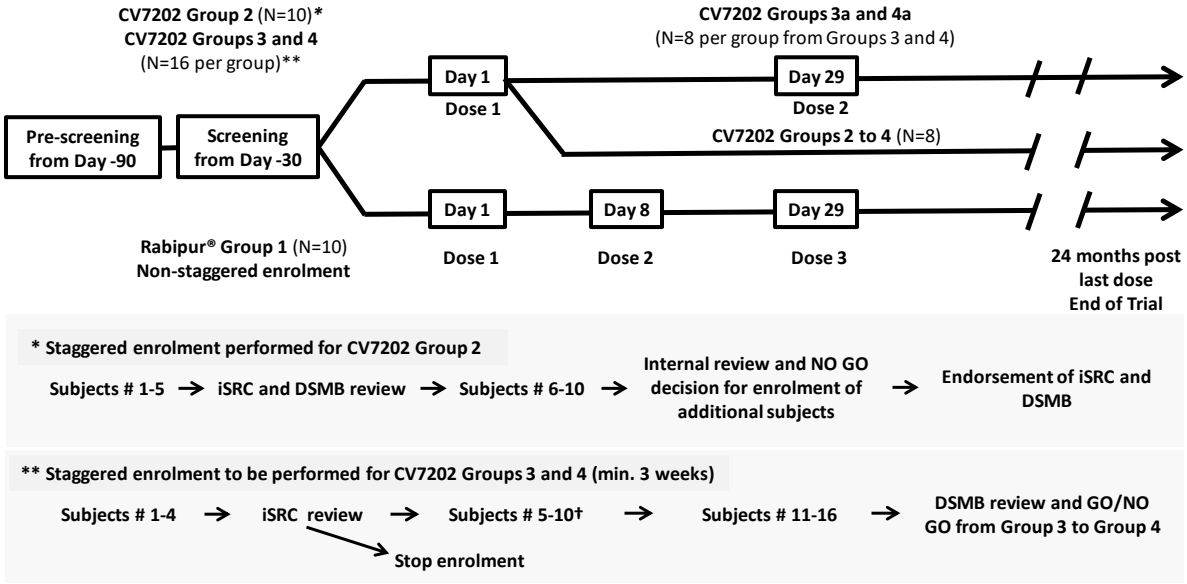
** Will be performed only on selected samples with VNT >0.5 IU/ml.

5 Trial Design

5.1 Overall Design

This is a non-randomized, open label, controlled, dose-escalation, phase I clinical trial to evaluate the safety, reactogenicity and immunogenicity of one or two i.m. administrations of candidate rabies mRNA vaccine CV7202 in healthy adult subjects. Approximately 52 subjects will be enrolled sequentially in up to 4 trial groups to receive either a dose of CV7202 containing different mRNA content or Rabipur®. In a first CV7202 group, 10 subjects have received a dose containing 5 µg mRNA. A dose of 1 or 2 µg mRNA will be administered to 2 additional groups of 16 subjects each, of whom 8 in each group will be administered a second dose 28 days later. A control group of 10 subjects will receive 3 doses of the licensed vaccine Rabipur® according to the manufacturer's recommendations. Safety and immunogenicity assessments will be made up to 2 years following the last dose administration. Specified safety data will be reviewed by an internal safety review committee (iSRC) and a data safety monitoring board (DSMB) on a pre-defined schedule.

Figure 5.1 CV-7202-104 Trial Design



† The number of subjects in this extended staggered enrollment may be further established by the investigator, sponsor or DSMB based on the data obtained in first 4 enrolled subjects.

5.1.1 Dose-finding Schedule, Enrolment Plan

Enrolment will be staggered in Groups 2 to 4 to ensure the safety of the participating subjects (Table 2.2). Enrolment into Group 1 (1.0 ml Rabipur®) will not be staggered, since the clinical safety of Rabipur® is well-established.

CV7202 Groups: In Group 2, the first 5 subjects sequentially received the first dose with a 2 working-day interval between subject #1 (e.g. Week 1 – Day 1 – Monday) and subjects #2 and #3 (e.g. Week 1- Day 3 – Wednesday) and were observed for 2 days. Subjects #4 and #5 received their first dose one week after subject #1 (e.g. Week 2 – Day 1 – Monday). Once the fifth subject in the group had been vaccinated and followed up for at least 2 working days, safety data for the first 5 subjects were

reviewed by the iSRC. Following iSRC approval, the remaining 5 subjects in the group were enrolled and received the first dose.

In Groups 3 and 4, the first 4 subjects will also be enrolled using a staggered approach. The first 4 subjects will sequentially receive the first dose with a 2 working-day interval between subject #1 (e.g. Week 1 – Day 1 – Monday) and subject #2 (e.g. Week 1- Day 3 – Wednesday) and will be observed for 2 days. A phone call will be performed after 2 days to collect safety information. Subjects #3 and #4 will receive their first dose at the earliest one week after subject #1 (e.g. Week 2 – Day 1 – Monday). All data obtained from these sentinel subjects (at least until 2 days after the vaccinations) must be entered continuously into the eCRF, at the latest within 24 hours, to allow a timely safety assessment. Once the fourth subject in the group has been vaccinated and followed up for at least 2 working days, safety data recorded in the eCRF for the first 4 subjects will be reviewed by the iSRC. Following iSRC approval, the remaining 12 subjects in the group will be enrolled and receive the first dose. In addition, the staggered enrolment may be extended to the subsequent subjects to be enrolled in Groups 3 and 4. The number of subjects in this extended staggered enrolment may be further established by the investigator, sponsor or DSMB based on the data obtained in earlier enrolled subjects in these groups. The DSMB will review safety data for an observation period of 28 days following administration of the first dose for all subjects in each dose group prior to enrolment into the next dose group (i.e. from the 1 µg dose level Group 3 to the 2 µg dose level Group 4). Before administration of the second dose of CV7202, the iSRC will review all available accumulated safety data from all subjects having already received a second dose.

Enrolment in each dose group can proceed as follows for a duration of a minimum of 7 weeks per group. A slower enrolment schedule can be followed in agreement with the investigator and sponsor, if needed with input from the iSRC or DSMB:

- **Week 1:** Start enrolment in Group 3 (up to 2 subjects). Subject #1 on Day 1, subject #2 on Day 3.
- **Week 2:** Enrol subjects #3 and 4 on Day 1 and prepare iSRC review of AEs and available safety data following 2 days' observation.
- **From Week 3:** Enrol the remainder of the subjects (i.e. 12 subjects for Groups 3 and 4). Extended staggered enrolment (e.g. for subjects #5 to 10 or beyond) can be implemented as needed.
- **From Week 7:** Collect solicited AEs, unsolicited AEs, SAEs and safety laboratory data, and prepare DSMB review.
- Favorable DSMB decision: Start the enrolment cycle for the next dose level group.

The staggered approach to dose administration does not apply to Dose 2.

5.1.2 Stopping Rules

For dose escalation (group)

At each planned safety review, safety data will be reviewed and a GO/NO GO decision made accordingly for enrolment of further subjects and administration of subsequent doses.

Enrolment or administration at the given dose level will be temporally halted and only continued after DSMB approval and approval by the competent authority following the occurrence of:

- Any related SAE in the opinion of the principal investigator (PI), the DSMB and/or the iSRC.
- Related severe AEs of the same kind in ≥ 20% of the subjects in one group with the following exceptions:
  - Transient grade 3 chills, fatigue, headache, fever, myalgia or arthralgia resolving within 24 hours to grade ≤2.
  - Transient grade 3 local AEs reducing to grade ≤2 within 48 hours.

Based on the review of the data, the DSMB will decide about temporary or permanent stopping of dosing in the given and eventually also lower dose groups (pertaining to the 2nd dose administration). After a temporary halt further measures for safety monitoring (i.e. additional safety visits including safety blood sampling at additional time points) may also be introduced based on DSMB recommendation.

For further CV7202 dose administration (subject)

Subjects must not receive a second dose of CV7202 in the event of:

- Occurrence of an allergic/anaphylactic reaction after the first dose.
- Any related SAE in the opinion of the PI, the DSMB and/or the iSRC.
- Any related severe (grade 3) AEs with the following exceptions:
  - Transient grade 3 chills, fatigue, headache, fever, myalgia or arthralgia resolving within 24 hours to grade ≤2.
  - Transient grade 3 local reactions resolving to grade ≤2 within 48 hours.

If these reactions occur, the subject must not receive additional vaccinations but is encouraged to continue in trial participation for safety reasons, including collection of safety blood samples. Immunogenicity assessments may be performed at the investigator's discretion and if the subject agrees.

5.1.3 Timing of Blood Collection for Safety and Immunogenicity Parameters

Blood samples will be drawn as follows:

- Safety assessments: Pre-screening, screening, Days 1, 2 or 3**, 8, 15, 29, 30 or 31**, 36, 57, Day 91, Month 6* (Day 181 [1-dose groups] and Day 209 [2-dose groups and Group 1 (Rabipur®)]) and Month 12* (Day 365 [1-dose groups] and Day 393 [2-dose groups and Group 1 (Rabipur®)]).

  ** In case a site visit is not possible due to the public health emergency related to COVID-19, the blood sample for safety assessment at Month 6 and Month 12 should be collected at Visit 14A and Visit 15A, respectively, only in case restrictive measures related to COVID-19 no longer prevent site visits (refer to Section 9.4.16 and 9.4.17 for details). If no blood sampling could be performed at Visit 15 and 15A (Month 12), the end-of-trial blood sample for safety assessment may be performed at Visit 17 (Month 24).*

- Immunogenicity assessments: Days 1, 2 or 3**, 8, 15, 29, 30 or 31**, 36, 43, 57, Day 91, Month 6* (Day 181 [1-dose groups] and Day 209 [2-dose groups and Group 1 (Rabipur®)]), Month 12* (Day 365 [1-dose groups] and Day 393 [2-dose groups and Group 1 (Rabipur®)]), Month 18* (Day 547) and Month 24* (Day 729).

  ** In case a site visit is not possible due to the public health emergency related to COVID-19, the blood sample for immunogenicity assessments should be collected at Visits A, only in case restrictive measures related to COVID-19 no longer prevent site visits (refer to Sections 9.4.16 to 9.4.19 for details).*

** Days 3 and 31 were planned in the original protocol and only apply to subjects in Groups 1 and 2 who were already enrolled and vaccinated before this protocol amendment was issued. Days 2 and 30 apply to all other subjects.

Refer to the schedule of activities in Table 2.1 and Section 9.5.

5.2 Subject and Trial Completion

Subjects will be enrolled at pre-screening (Day -90 to -1) to receive either CV7202 starting Day 1 as 1 dose or 2 doses (at least 28 days apart), or 3 doses of control vaccine (Rabipur®). Follow-up for safety and immunogenicity is planned up to 24 months after the last dose, therefore the expected duration of participation for each subject is approximately 24 months after the last dose.

5.3 End of Trial Definition

Trial end is defined as the point at which the last subject has completed the last visit.

5.4 Trial Data Review

An iSRC will evaluate all AEs on a pre-defined schedule in consultation with the PI. The roles and responsibilities of the iSRC will be described in the corresponding charter.

5.5 Data and Safety Monitoring Board

An independent DSMB (consisting of external independent vaccine experts) will review safety data (solicited and unsolicited AEs, SAEs and safety lab) on a regular basis and make recommendations about sequential enrolment of subjects into dose escalation groups.

The DSMB will monitor safety during the trial and can meet ad hoc to review potentially related SAEs, AESIs, other unexpected related severe AEs or safety signals identified by the sponsor or designee. Trial dose administration will be temporally halted for the given dose level and resume after DSMB and competent authority approval.

The roles and responsibilities of the DSMB will be described in the DSMB charter.

5.6 Scientific Rationale for Trial Design

The multi-cohort dose escalation trial design of CV-7202-104 is considered appropriate to investigate safety and immunogenicity of CV7202 in a FIH trial. The dose range, route of administration and regimen were initially selected based on non-clinical studies which are further described in the IB [17]. A licensed vaccine,

Rabipur® was selected as an active control for safety, reactogenicity and immunogenicity.

5.7 Justification for Dose

The clinical dose range of 5-200 µg was justified based on data from two repeat dose toxicity studies (in rat and rabbit) and local reactogenicity and immunogenicity data from a pharmacology study in cynomolgus monkeys.

The no observed adverse effect level (NOAEL) of CV7202 was calculated for both rat and rabbit. Rabbit was the most sensitive species. Doses intended for the phase 1 study were evaluated using two different approaches based on the NOAEL in rabbit. Normalization of dose based on a direct mg/kg conversion of the NOAEL provided a human equivalent dose of 800 µg which is approximately 4-fold greater than the highest anticipated clinical dose of 200 µg. Allometric scaling provided a conservative maximum recommended starting dose of 26 µg which is approximately 5-fold the starting dose of 5 µg. Furthermore, toxicology studies evaluated animals which were administered 4 injections at weekly intervals while human subjects will receive a single injection or two injections at least 28 days apart. Doses up to 210 µg in cynomolgus monkeys were associated with only minimal to mild reactogenicity at the injection sites.

Pharmacology data from a study of cynomolgus monkeys support the clinical dose range. After a single i.m. injection in cynomologus monkeys of 1 µg CV7202, VNTs above the threshold of protection were observed as early as Day 28 and were still detected six months later. By extrapolation, a dose of 1 µg in a monkey (0.3 µg/kg) would represent an equivalent dose of 5-15 µg in a human. Thus, it is possible that CV7202 will elicit an immune response in human subjects from the initially defined clinical starting dose of 5 µg.

Based on the reactogenicity and immunogenicity results from the first 10 subjects vaccinated with CV7202 at the 5 µg dose level in the current trial, the dose ranges to be tested in the other groups have been lowered to 1 and 2 µg.

5.8 Benefit-Risk Assessment

5.8.1 Possible Risks and Adverse IMP Reactions

No final clinical data for CV7202 are available to date.

Evidence from non-clinical studies shows that CV7202 is well-tolerated in relevant animal species and no safety risks have been identified.

The LNP-formulated RNActive® rabies vaccine (CV7202) for i.m. administration is being tested for the first time in humans. As with every vaccination and based on previous clinical experience with other RNActive® vaccines as well as preliminary data after administration of CV7202 to the first 10 subjects vaccinated with 5 µg of CV7202 in the current trial, local reactions, i.e. pain, redness, itching and swelling at the injection site, and systemic AEs, i.e. chills, fatigue, headache, fever, myalgia, arthralgia, nausea/vomiting and diarrhea, are expected side effects that typically resolve within 24 hours after the vaccination with or without corrective treatment with antipyretics [18, 19, 20, 21].

As for every vaccine, the occurrence of allergic/anaphylactic reactions cannot be excluded and emergency equipment for the treatment of such reactions must be available at the trial site. These events are unexpected and constitute a potential important medical risk. So far, no allergic/anaphylactic reactions have been observed in the completed and ongoing clinical trials after repeated administration of protamine-formulated RNActive® vaccines, nor after administration of CV7202 to the first 10 subjects vaccinated with 5 µg of CV7202 in the current trial.

During the very early stages of manufacture of CV7202, ampicillin is used. Although there is no evidence of residual ampicillin in the final investigational medicinal product (IMP), subjects with a previous class I allergic reaction to beta-lactam antibiotics should be excluded from vaccination with CV7202 as a measure of precaution.

Developmental toxicity studies have not been performed for CV7202. No histopathological alterations in the reproductive organs were identified in the local tolerance or repeat-dose toxicology studies in rat or rabbit, and toxicologically relevant levels of RNA were not detected in reproductive organs in the biodistribution study. Therefore, the teratogenicity risk is deemed low. However, given that human data on pregnancies is not available, the teratogenic risk associated with CV7202 administration cannot be ruled out at this moment. For this reason, inclusion of female subjects of childbearing potential requires use of a highly effective contraceptive measure from 2 weeks before the first administration of the test vaccine until 3 months following the last administration.

5.8.2 Adverse Events of Special Interest

Due to the theoretical possibility of non-specific immune stimulating properties of CV7202, it cannot be excluded that pre-existing potential immune mediated diseases (pIMDs) may be aggravated, become clinically apparent for the first time or triggered after vaccination with CV7202. Such reactions have been very rarely described after administration of other vaccines but the causal relationship between vaccination and the induction or aggravation of pIMDs is uncertain and is therefore a theoretical risk. These events are considered unexpected for CV7202.

If suspected potential immune-mediated reactions should occur in a subject who received CV7202, a diagnostic workup should be performed by a specialist depending on the type of suspected reaction (e.g. endocrinologist for suspected autoimmune thyroiditis) and these conditions will be monitored and documented throughout the trial. AEs with a suspected pIMD etiology will be considered AESI.

A list of AESIs will be closely followed throughout the trial (please see Appendix 10).

5.8.3 Drug and Vaccines Interactions

CV7202 has not been investigated in combination with other drugs or vaccines.

Given the mechanism of action which relies on building up a protective immune response, it is expected that immunosuppressive drugs like steroids may inhibit the desired pharmacological effect of the induction of a specific immune response against the rabies virus G protein. Similarly, drugs that enhance the immune response like certain cytokines (interferon-α, interleukin 2) may increase the response to the vaccines which could theoretically result in increased efficacy but also in an increased risk of toxicity.

5.8.4 Precautions and Warnings

CV7202 is an IMP. It should only be administered to subjects who have given written consent (see Appendix 2, Appendix 13, Appendix 15 and Appendix 16) to participate in a clinical trial for which a protocol has been approved by the sponsor, investigator, and any relevant authorities and ethics committees.

CV7202 is intended strictly for i.m. injection by needle-syringe in the deltoid area (preferably in the non-dominant arm) and must not be injected subcutaneously, intradermally or intravenously. The instruction for injection described in the trial-specific handling manual must be followed. An intravascular injection is highly unlikely at this site due the lack of larger blood vessels. However, a blood aspiration test should be performed prior to i.m. needle injection of CV7202 as a measure of precaution.

Since there is a theoretical risk of anaphylactic reactions, the vaccine must only be administered if emergency equipment for the treatment of anaphylactic reactions (intravenous fluids, corticosteroids, H1 and H2 blocking agents, epinephrine, equipment for cardiopulmonary resuscitation) is readily available and subjects must remain under direct supervision of personnel trained in the treatment of these reactions for 4 hours following administration of the trial IMP.

If anaphylaxis or severe hypersensitivity reactions occur following IMP administration, no further doses should be given.

5.8.5 Recognition and Treatment of Possible Overdose and Adverse IMP Reactions

No toxic effects are expected from current clinical and pre-clinical experience. Possible local reactions (pain) or systemic AEs (e.g. fever, headache, chills) can be treated symptomatically with physical measures, paracetamol or non-steroidal anti-inflammatory drugs, at the investigator’s discretion.

5.8.6 Benefit-Risk Conclusion

In conclusion, CV7202 is expected to be safe at doses considered for the clinical trial. The expected adverse effects do not usually constitute important medical risks.

Potential important medical risks associated with CV7202 have been identified based on the mechanism of action, and can be managed in a phase I setting should they occur.

6 Trial Population

6.1 Inclusion Criteria

Subjects must satisfy the following criteria at trial entry:

1. Healthy male and female subjects aged 18 to 40 years inclusive.

   Healthy Subject is defined as an individual who is in good general health, not having any mental or physical disorder requiring regular or frequent medication.
2. Expected to be compliant with protocol procedures and available for clinical follow-up through the last planned visit.
3. Physical examination and laboratory results without clinically significant findings.
4. Body Mass Index (BMI) ≥18.0 and ≤32.0 kg/m2.
5. Females: At the time of screening, negative human chorionic gonadotropin (hCG) pregnancy test (serum) for women presumed to be of childbearing potential on the day of enrolment. On Day 1 (pre-vaccination): negative urine pregnancy test (hCG), (only required if the screening visit serum pregnancy test was performed more than 3 days before).
6. Females of childbearing potential must use acceptable methods of birth control from 2 weeks before the first administration of the test vaccine until 3 months following the last administration. The following methods of birth control are acceptable when used consistently and correctly:

   - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal);
   - progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable);
   - intrauterine devices (IUDs);
   - intrauterine hormone-releasing systems (IUSs);
   - bilateral tubal occlusion;
   - vasectomized partner;
   - sexual abstinence (periodic abstinence [e.g., calendar, ovulation, symptothermal and post-ovulation methods] and withdrawal are not acceptable).

   Refer to the Clinical Trial Facilitation Group (CTFG) recommendations on contraception and pregnancy testing for further details [23].
7. Males must use reliable forms of contraception (condom) from the moment of the first administration of the test vaccine until 3 months following the last administration and must refrain from sperm donation from the moment of the first administration of the test vaccine until 3 months after the last administration.

6.2 Exclusion Criteria

Any trial subject who meets any of the following criteria will not qualify for entry into the trial:

1. Use of any investigational or non-registered product (drug or vaccine) other than the trial vaccine within 4 weeks preceding the administration of the trial vaccine, or planned use during the trial period.
2. Receipt of any other vaccines within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to enrolment in this trial or planned receipt of any vaccine within 28 days of any trial vaccine administration.
3. Receipt of any licensed or investigational rabies vaccine prior to the administration of the trial vaccine.
4. Planning to travel to regions/countries for which rabies vaccinations are recommended or where high risk of infection exists according to travel recommendations by the German Society of Tropical Medicine and International Health during the trial and up to the end of the trial.
5. Any treatment with immunosuppressants or other immune-modifying drugs within 6 months prior to the administration of the trial vaccine or planned use during the trial, with the exception of inhaled and nasal steroids, or topically-applied steroids.
6. Any medically diagnosed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination, including human immunodeficiency virus (HIV) infection, hepatitis B virus (HBV) infection and hepatitis C virus (HCV) infection.
7. History of a potential immune mediated disease.
8. Administration of immunoglobulins (Igs) and/or any blood products within the 3 months preceding the administration of any dose of the trial vaccine.
9. Presence or evidence of significant acute or chronic, uncontrolled medical or psychiatric illness.
10. Known allergy to any component of CV7202 such as type I allergy to beta-lactam antibiotics or Rabipur®.
11. Evidence of current alcohol or drug abuse.
12. History of any neurological disorders or seizures including Guillain-Barré syndrome (GBS), with the exception of febrile seizures during childhood.
13. Foreseeable non-compliance with protocol as judged by the investigator.
14. For females: Pregnancy or lactation.
15. History of any life-threatening anaphylactic reactions.
16. Subjects with impaired coagulation or any bleeding disorder in whom an i.m. injection or a blood draw is contraindicated.
17. Known relatives of site research staff working on this trial.

6.3 Dose Modification / Vaccine Delay Recommendations

After enrolment, subjects may encounter clinical circumstances that warrant a delay of trial dose administration. These situations are listed below:

- Subjects with a clinically significant (≥ grade 2) active infection or other acute disease (as assessed by the investigator) or temperature >38.0°C (>100.4°F), within 3 days of intended trial vaccination. Further dose administration should be delayed until the active infection or other acute disease has recovered to ≤ grade 1 or the subject is without temperature >38.0°C (>100.4°F) for at least 3 days.

In the event that a subject meets a criterion for delay of vaccination, the subject may receive the trial dose once the window for delay has passed (Table 2.1) if clinically appropriate to vaccinate in the judgment of the investigator and the time windows of the protocol can be respected.

There are also circumstances under which receipt of further vaccines is a contraindication in this trial (see section 5.1.2). If these reactions occur, the subject(s) must not receive additional vaccinations but is/are encouraged to continue in trial participation for safety reasons, including collection of safety blood samples. Immunogenicity assessments may be performed also, at the investigator's discretion and if the subject agrees.

6.4 Screen Failures

The investigator must account for all subjects who sign an informed consent. If the subject is found to be not eligible at the screening visit (i.e. did not meet all inclusion criteria or did meet one or more exclusion criteria), the investigator should document this in the subject's source data only. Re-screening is allowed if the reason for ineligibility is a transient event.

7 Discontinuation/Withdrawal Criteria

Participation in the trial is strictly voluntary. A subject has the right to withdraw from the trial at any time and for any reason. The investigator has the right to withdraw a subject from further trial vaccine administration and/or the trial if this is considered in the subject's best interest or is as a result of a protocol deviation.

For discontinuations due to an AE, every effort should be made to document the outcome of the event.

7.1 Discontinuation of Trial Vaccine Administration and/or Blood Sampling

The primary reason for discontinuation of further administrations of CV7202 will be recorded in the subject's electronic case report form (eCRF) according to the following categories:

- The subject withdraws consent. The subject wishes to withdraw from the trial. The reason for withdrawal, if provided, should be recorded in the eCRF.

Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (i.e. withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category).

- AE (including known side effects of the test product). If discontinuation is due to an AE possibly related to CV7202, Rabipur® or the trial procedures, the subject must be followed-up by additional examinations according to the medical judgment of the investigator until the condition is resolved or the investigator deems further observations or examinations to be no longer medically indicated.
- Change in the subject's overall medical status prohibiting further participation.
- Pregnancy (Appendix 12). Any subject who, despite the requirement for adequate contraception, becomes pregnant during the trial will not receive further trial vaccines. The site should maintain contact with the pregnant subject and complete a "Clinical Trial Pregnancy Form" as soon as possible. In addition, the subject should be followed-up until the birth of the child, or spontaneous or voluntary termination. When pregnancy outcome information becomes available, the information should be captured using the same form. The subject should be reported as an IMP discontinuation and the reason (e.g. pregnancy) should be given.
- Trial terminated by the sponsor (in which case the minimum safety follow-up of one year would be performed).
- Major protocol deviation.
- Other.

Note: The specific reasons should be recorded in the "specify" field of the eCRF.

Subjects who will not receive further doses of CV7202 will be encouraged to continue participation until the end of the trial for safety assessments. Immunogenicity assessments may be performed at the investigator's discretion, if the subject agrees.

7.2 Withdrawal from the Trial

Withdrawal from the trial is recorded according to the following criteria:

- Where continued participation jeopardizes the subject's health, safety or rights.
- The subject has experienced an AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the AE. The reasons for not performing further safety or immunogenicity assessments should be documented.
- The subject did not return to the trial site and multiple attempts (at least 3) to contact the subject were unsuccessful (lost to follow-up).
- The subject wishes to withdraw from the trial. The reason for withdrawal, if provided, should be recorded.

Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (i.e. withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category).

Any subject who prematurely terminates participation and who has received at least one vaccination will undergo the same procedures as for the final visit, unless such procedures are considered to pose unacceptable risk to the subject.

Discontinued or withdrawn subjects will not be replaced, except in the case of dropouts occurring before Visit 4 for the first 4 subjects from Groups 3 or 4, unless the affected subjects have experienced any AE fulfilling the stopping criteria and the DSMB does not approve the replacement (section 5.1.2).

7.3 Trial Termination

The sponsor reserves the right to terminate the trial at any time. Possible reasons for trial termination are:

- Safety reasons: the incidence of AEs in this or any other trial using a related IMP indicating a potential health risk for the subjects.
- New scientific knowledge becomes known that makes the objectives of the trial no longer feasible/valid.
- The trial site is unlikely to be able to recruit sufficient subjects within the agreed time frame.
- The trial site does not respond to trial management requests.
- Repeated protocol deviations.
- Unsafe or unethical practices.
- Administrative decision.

Following a trial termination decision, the investigator must contact all subjects within a time period set by the sponsor. All trial materials must be collected and relevant documentation completed to the greatest extent possible.

7.4 Lost to Follow-Up

A minimum of 3 attempts to contact subjects who have not returned for the final visit or discontinuation visit should be made and documented. If a subject is lost to follow-up before resolution of related SAEs or AEs indicating potential immune mediated disease, the sponsor may consider further attempts to contact the subject in order to collect follow-up safety information.

8 Clinical Trial Material Management

The following sections describe the procedures for clinical trial material management for protocol CV-7202-104. Refer to the protocol CV-7202-104 Handling Manual for further information on CV7202 and to the product information leaflet [24] for additional information concerning Rabipur®.

8.1 Trial Vaccine and Formulation

The IMP is composed of the API, CV7202: RABV-G encoding mRNA, and [redacted]The IMP is provided as a sterile solution in a 2 ml glass vial with rubber stopper closure.

Mixing of CV7202 and 0.9 % sodium chloride (NaCl) to produce dosing solutions for i.m. injection will occur at the local pharmacy according to the handling protocol provided by CureVac. The volume to be administered is 0.5 ml for Group 2, 0.1 ml for Group 3 and 0.2 ml for Group 4, corresponding to dose levels of 5 µg, 1 µg and 2 µg mRNA, respectively.

8.2 Control Vaccine

Rabipur® (GSK Vaccines GmbH, Marburg, Germany) is a licensed rabies vaccine* (inactivated, strain Flury LEP) ≥2.5 IU / 1.0 ml reconstituted dose.

This vaccine contains residues of polygeline, chicken proteins (e.g., ovalbumin), human serum albumin, and may contain traces of neomycin, chlortetracycline and amphotericin B.

** Produced on purified chick embryo cells (PCEC).*

8.3 Route of Administration

Injections will be performed i.m. by needle in the deltoid area (non-dominant arm), in all groups.

8.4 Trial Groups

The subjects will be distributed among the different groups to receive CV7202 or Rabipur® (Table 8.1).

Table 8.1 Protocol CV-7202-104 Dose regimen

	Trial Product	Composition	Dosing		
			Day 1	Day 8	Day 29
			N	N	N
Group 1	Rabipur®	N/A	10	10	10
Group 2*	CV7202	5 µg mRNA	**10**	N/A	**N/A**
Group 3 • Group 3a**		1 µg mRNA	**16**		**8**
Group 4 • Group 4a**		2 µg mRNA	**16**		**8**
Total CV7202			42		16

* Note that enrolment in Group 2 was already completed at the time this protocol amendment was issued.
** **'a'** groups are a subset consisting of 8 subjects of Groups 3 and 4 scheduled to receive a first dose on Day 1 and a second dose on Day 29.

8.5 Method of Trial Vaccine Assignment

This trial is non-randomized. Eight vaccinated subjects in Groups 3 and 4 will receive two doses of CV7202 and the remaining 8 subjects in these groups will receive one dose of CV7202.

8.6 Blinding

This trial is open label.

8.7 Trial Vaccine and Supplies Accountability

It is the responsibility of the investigator to ensure that current and accurate records of trial supplies received, stored and dispensed at the site are maintained using appropriate forms according to applicable regulations and guidelines. The trial supplies must be stored under the recommended storage conditions, locked with restricted access (refer to the Handling Manual). Authorized personnel must dispense the vaccine at the trial site and in accordance with the protocol and applicable regulations and guidelines.

A dispensing log for CV7202 must be kept up-to-date at the trial site with the following information:

a. Dates and quantities of CV7202 received from CureVac.

b. Unique subject identifier.

c. Date and quantity of trial vaccine dispensed to each subject.

d. Initials of the person preparing the dose.

e. Initials of the person administering the vaccine.

These accountability forms must be readily available for inspections and are open to regulatory inspection at any time.

8.8 Vaccine Compliance

The investigator will record all injections of trial vaccine (CV7202 and Rabipur®) given to the subject in the electronic eCRF.

8.9 Concomitant Therapy and Vaccines

Concomitant medication and vaccines must be recorded in the subject's eCRF.

If post-exposure vaccination for rabies is needed, the subject should be discontinued from receiving a further trial dose, but followed-up for safety assessments.

For additional information, refer to section 6.2.

8.10 Therapy leading to elimination

If a trial subject requires therapy listed as an exclusion criterion in section 6.2 and which cannot be delayed, discontinuation would be considered to ensure integrity of the trial data, following individual case review. Medications taken for prophylaxis (i.e. intended to prevent the onset of symptoms following vaccination) are not allowed.

8.11 Treatment after the End of the Trial

No post-trial care will be provided.

9 Trial Assessments and Procedures

The following sections describe the trial procedures and data to be collected. Additional trial-related information is provided in section 12, Appendix 1 to Appendix 17.

9.1 Adverse Events

Definitions and procedures for recording, evaluating, follow-up, and reporting of AEs are provided in Appendix 11. The intensity of AEs will be graded in the following manner:

Absent:	• Grade 0	• No AE
Mild:	• Grade 1	• An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
Moderate:	• Grade 2	• An event that causes sufficient discomfort to interfere with normal everyday activities.
Severe:	• Grade 3	• An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

Solicited AEs will be collected on the day of vaccination and the 7 subsequent days (Days 1-8) and the intensity grading will be applied (Table 9.1 and Table 9.2). By definition, all local solicited symptoms are considered related to vaccination.

Unsolicited AEs will be collected on the day of vaccination and the 28 subsequent days (Days 1-29).

Table 9.1 Intensity Grading for Solicited Local AEs (Days 1 to 8)

AE	Grade	Definition
Pain at injection site*	0	Absent
	1	Does not interfere with activity
	2	Interferes with activity and/or repeated use of non-narcotic pain reliever >24 hours
	3	Prevents daily activity and/or repeated use of narcotic pain reliever
Redness*	0	≤2.5 cm
	1	2.5 – 5 cm
	2	5.1 – 10 cm
	3	>10 cm
Swelling*	0	≤2.5 cm
	1	2.5 – 5 cm and does not interfere with activity
	2	5.1 – 10 cm or interferes with activity
	3	>10 cm or prevents daily activity
Itching	0	Absent
	1	Mild, no interference with normal activity
	2	Moderate, some interference with normal activity
	3	Significant, prevents normal activity

*FDA toxicity grading scale [25].

Table 9.2 Intensity Grading* for Solicited Systemic AEs (Days 1 to 8)

AE	Grade	Definition
Fever	0	<38°C
	1	≥38 – 38.4°C
	2	≥38.5 – 38.9°C
	3	≥39°C
Headache	0	Absent
	1	Mild, no interference with normal activity
	2	Moderate, some interference with normal activity and/or repeated use of non-narcotic pain reliever >24 hours
	3	Significant; any use of narcotic pain reliever and/or prevents daily activity
Fatigue	0	Absent
	1	Mild, no interference with normal activity
	2	Moderate, some interference with normal activity
	3	Significant, prevents normal activity
Chills	0	Absent
	1	Mild, no interference with normal activity
	2	Moderate, some interference with normal activity
	3	Severe, prevents normal activity
Myalgia	0	Absent
	1	Mild, no interference with normal activity
	2	Moderate, some interference with normal activity
	3	Significant, prevents normal activity
Arthralgia	0	Absent
	1	Mild, no interference with normal activity
	2	Moderate, some interference with normal activity
	3	Significant, prevents normal activity
Nausea/ Vomiting	0	Absent
	1	Mild, no interference with activity and/or 1 – 2 episodes/ 24 hours
	2	Moderate, some interference with activity and/or >2 episodes/ 24 hours
	3	Severe, prevents daily activity, requires outpatient i.v. hydration
Diarrhea	0	Absent
	1	2 – 3 loose stools or <400 g/24 hours
	2	4 – 5 stools or 400 – 800 g/24 hours
	3	6 or more watery stools or >800 g/24 hours or requires outpatient IV hydration

*FDA toxicity grading scale [25]; i.v. = Intravenous.

Laboratory data will be graded according with the FDA toxicity grading scale [25] and the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 [26]. These guidelines however are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

AEs with a suspected immune mediated disease etiology will be considered AESIs. The list of AESI is provided in (Appendix 10).

Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting of AEs are provided in Appendix 11.

9.2 Safety Assessments

The following safety assessments apply to all subjects in Groups 1 to 4:

All vaccinations will be administered on an outpatient basis. All subjects will be monitored for 4 hours following administration of the trial IMP. Vital signs must be within normal ranges or have returned to pre-vaccination levels (pre-vaccination values ± 15% or no clinically relevant deviation from pre-vaccination values) for the subject to be discharged.

All subjects will undergo a vaccination site reactogenicity assessment (injection site pain, redness, swelling and itching) at 1 hour post vaccination on the day of vaccination (Day 1, Day 8 [Rabipur® Dose 2] and Day 29 [Rabipur® and Groups 3a and 4a]) and 1 or 2 days after each vaccination (Day 2 or 3, Day 10 [Rabipur® Dose 2] and Day 30 or 31 [Rabipur® and Groups 3a and 4a]). Note that Days 3 and 31 were planned in the original protocol and only apply to subjects in Groups 1 and 2 who were already enrolled and vaccinated before this protocol amendment was issued. Days 2 and 30 apply to all other subjects. For those subjects, a phone call will be performed to collect safety information 2 days after each vaccination.

Local reactions at 1 hour post-vaccination will be assessed on an intensity scale of absent, mild, moderate and severe. The trial personnel will record these in the eCRF.

Diary cards will be distributed to all subjects and used to collect solicited local (injection site pain, redness, swelling and itching) and systemic (fever, nausea/vomiting, diarrhea, headache, fatigue, myalgia and arthralgia) AEs on the day of vaccination and the 7 subsequent days (Days 1 to 8, Day 8 to 15 [Rabipur® Dose 2] and Days 29 to 36). Local reactions and systemic events will be assessed on an intensity scale of absent, mild, moderate and severe. The diary card will be reviewed on Day 2 or 3, 8, 10, 15, 29, 30 or 31, 36, 43 and 57. In case of related grade 3 solicited or unsolicited AEs reported for more than 1 day on the diary card, the subject will be interrogated to establish the total duration of the AE and this information will be recorded in the medical file. Unsolicited AEs occurring on the day of vaccination (Day 1, Day 8 and Day 29) and for the following 28 days will be recorded by the subject on the diary card.

The occurrence of AEs (serious and non-serious) will be assessed by non-directive questioning of the subject at each visit. AEs volunteered by the subject during or between visits as subject diary card entries or detected through observation, physical examination, laboratory test, or other assessments during the entire trial, will be documented. Subjects will be instructed that they must immediately report any AEs with serious symptoms, subjective complaints or objective changes in their well-being to the investigator or the clinic personnel, regardless of the perceived relationship between the event and the test vaccine.

SAEs, MAAEs and AEs leading to trial or vaccine withdrawal will be collected up to 12 months after the last dose administration. After Visit 15 (Month 12), only SAEs and MAAEs that according to the investigator are considered to be related to study vaccination will be collected.

Intercurrent medical conditions and AESIs will be collected throughout the trial.

Clinical laboratory testing for safety evaluations are provided in Appendix 6. Definitions and procedures for recording, evaluating, follow-up and reporting of AEs are provided in Appendix 11.

9.3 Immunogenicity Assessments

The following immunogenicity assessments will be made:

Rabies-specific serum VNTs will be measured using the WHO-recommended rapid fluorescent foci inhibition test (RFFIT) before and after vaccination on Days 1, 8, 15, 29, 36, 43, 57, 91, and 6, 12, 18 and 24 months post-last dose.

The percentages of vaccine recipients with VNTs ≥0.5 IU/ml (WHO-recommended threshold correlating with protective immune responses) will be determined for each trial group. An antibody titer of 0.5 IU/ml serum is viewed as a surrogate of protection and defines seroconversion [26]. GMTs by treatment group will be calculated based on the VNTs on Days 1, 8, 15, 29, 36, 43, 57, 91, and 6, 12, 18 and 24 months post-last dose. VNTs assessments will be performed in a GCP-compliant laboratory.

Note that VNTs assessments at 18 and 24 months after the last vaccination will only be performed in subjects with detectable RABV-G-specific IgG at 6 months after the last vaccination or Day 91 if the Month 6 blood sample is not available.

RABV-G-specific IgM, IgG and IgA serum antibody levels will be measured by enzyme-linked immunosorbent assay (ELISA) on Days 1, 8, 15, 29, 36, 43, 57, 91, and 6 and 12 months post-last dose. In addition, RABV-G-specific IgG serum antibody levels will be measured at 18 and 24 months after the last vaccination in subjects with detectable RABV-G-specific IgG at 6 months after the last vaccination or Day 91 if the Month 6 blood sample is not available.

Additional immune-related effects will be assessed by exploratory analyses in peripheral blood samples, including measurements of serum cytokines, chemokines, and other soluble factors. These analytes include but are not limited to chemokine (C-X-C motif) ligand (CXCL)10, chemokine (CC motif) ligand (CCL)3, interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) on Days 1 (at pre-vaccination and 4 hours post-vaccination), 2 or 3 and 8 after each vaccination. Gene expression changes in peripheral blood will be determined by transcriptome profiling on Days 1 (at pre-vaccination), 2 or 3 and 8 after each vaccination. Cytokine assessments and transcriptome profiling will only be performed in the first 5 subjects in Group 2 (on Day 3) and all subjects in Groups 3 and 4 (on Day 2). Note that Day 3 post-vaccination was planned in the original protocol and only applies to subjects in Group 2 who were already enrolled and vaccinated before this protocol amendment was issued. Day 2 post-vaccination applies to all other subjects.

RABV-G-specific $CD4^+$ and $CD8^+$ T-cell responses will be determined by intracellular cytokine staining after 6-hour incubation of PBMCs in the presence of overlapping peptides covering the open reading frame of RABV-G on Days 1, 8, and 36. The groups will be tested in their entirety at Day 91 and 6 and 12 months post-last dose if there is a significant increase in T-cell response at Day 8 or 36 compared to baseline.

RABV-G-specific circulating B cells will be determined in PBMC samples by enzyme-linked immunospot (ELISpot) assay after short-term cell culture on Days 1, 8 and 36. The groups will be tested in their entirety at Day 91 and 6 and 12 months post-last dose if there is a significant increase in B-cell response at Day 8 or 36 compared to

baseline. Lymphocyte phenotyping will be performed by conventional flow cytometry or cytometry by time of flight (CyTOF).

The humoral immune response against RABV-G will be further characterized by immune receptor sequencing of peripheral B cells, on Days 1, 8, 29, 36, 57, 91, and 6 and 12 months post-last dose in a subset of subjects; and measurement of antibody affinity and avidity, measurement of VNTs against additional heterologous lyssavirus strains and identification of epitopes recognized by RABV-G-specific antibodies, on Days 1, 15, 43, and 12 months post last dose, on selected samples with VNT >0.5 IU/ml.

Additional exploratory testing, not defined in the objectives/endpoints, may be performed to further characterize the vaccine or immune response, including the development or improvement of tests related to the disease or the trial vaccines that will allow more reliable measurement of the response to the trial vaccines.

9.4 Trial Procedures

For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. Refer to the Schedule of Activities (Table 2.1).

9.4.1 Visit 1 (Pre-screening Visit, Days -90 to -1)

Pre-screening visit activities can occur between 90 and 1 days prior to vaccination.

- Signed informed consent must be obtained prior to the subject entering into the trial, and before any protocol-directed procedures are performed.

The following procedures will be performed during the pre-screening visit:

- Collection of demographic information.
- Vital signs check (body temperature, pulse, blood pressure).
- Record medical history, including details of treatments for re-occurring conditions.
- Review of eligibility criteria. See sections 6.1 and 6.2
- Safety assessments (SAEs, intercurrent medical conditions, AEs leading to trial withdrawal, AESIs and MAAEs).
- Blood draw (section 9.5) for:
    - Thyroid-stimulating hormone (TSH), thyroid antibodies, antinuclear antibody (ANA) (~3 ml). Blood drawn at the pre-screening visit will be kept for retrospective measurement of TSH, thyroid antibodies and ANA following the occurrence of clinical autoimmune events (other autoantibodies might be investigated as well depending on the clinical autoimmune event).

9.4.2 Visit 2 (Screening Visit, Days -30 to -1)

Screening visit activities can occur between 30 and 1 day prior to vaccination and may be performed on the same day as the Pre-Screening visit. The following procedures will be performed during the screening visit:

- Review of eligibility criteria. See sections 6.1 and 6.2.
- Serum pregnancy test (hCG) (~2 ml) for female subjects of childbearing potential.

- Physical examination (including weight, height, and general condition).
- 12-lead electrocardiogram (ECG).
- Assessment of concomitant medications/vaccinations.
- Safety assessments (SAEs, intercurrent medical conditions, AEs leading to trial withdrawal, AESIs and MAAEs).
- Blood draw (section 9.5) for safety laboratory (~9 ml).

9.4.3 Visit 3 (Vaccination Dose 1 CV7202 or Dose 1 Rabipur®, Day 1)

The following procedures will be performed during Visit 3:

- Review of eligibility criteria (sections 6.1 and 6.2).
- Review of criteria for vaccine delay (section 6.3).
- Urine pregnancy test for female subjects of childbearing potential, unless the serum pregnancy test was performed less than 3 days before.
- Physical examination (including weight and general condition) and vital signs check (body temperature, pulse, blood pressure).
- Blood draw for:
  - Safety laboratory (~9 ml).
  - Immunogenicity – VNTs (~18 ml), IgM/IgG/IgA (~6 ml), PBMCs* for CMI (~60 ml), cytokine assessment (~6 ml at pre-vaccination and ~6 ml at 4 hours post-vaccination [CV7202 groups only]), transcriptome profiling (~10 ml at pre-vaccination [CV7202 groups only]), immune receptor sequencing (~5 ml).

    * PBMCs will be taken for a subset of the first 5 subjects in Group 2 and all subjects in Groups 3 and 4.
- **Vaccination (Dose 1 CV7202 or Dose 1 Rabipur®)**.
- Post-injection vaccination site reactogenicity assessment after 1 hour for all subjects. Note that all subjects need to remain at the site for 4 hours after vaccination for safety monitoring. Vital signs will be then re-checked and have to be within normal ranges or have returned to pre-vaccination levels for the subject to be discharged.
- Subjects will be issued with diary cards to record solicited AEs occurring on the day of vaccination and the following 7 days. Unsolicited AEs occurring on the day of vaccination and for the following 28 days will also be recorded by the subject on the diary card. Subjects will be instructed on how to complete the diaries.
- Safety assessments (solicited AEs, unsolicited AEs, SAEs, intercurrent medical conditions, AEs leading to trial or vaccine withdrawal, AESIs and MAAEs, concomitant medications and vaccinations).

9.4.4 Visit 4 (Day 2 or 3)

The following procedures will be performed during Visit 4:

- Physical examination (including weight and general condition) and vital signs check (body temperature, pulse, blood pressure).

- Post-injection vaccination site reactogenicity assessment.
- Diary card review and reminder.
- Safety assessments (solicited AEs, unsolicited AEs, SAEs, intercurrent medical conditions, AEs leading to trial or vaccine withdrawal, AESIs and MAAEs, concomitant medications and vaccinations).
- Blood draw for:
  - Safety laboratory (~9 ml).
  - Immunogenicity* – cytokine assessment (~6 ml), transcriptome profiling (~10 ml) only for CV7202 groups.

    * PBMCs will be taken for a subset of the first 5 subjects in Group 2 and all subjects in Groups 1, 3 and 4.

It should be noted that for subjects enrolled in the trial before Protocol Amendment 1 became effective, Visit 4 occurred on Day 3 as planned in the original protocol

9.4.5 Phone call (Day 3)

A phone call should be performed on Day 3 for the **CV7202 groups only** to collect the following safety information:

- Any solicited AEs (including duration in case of grade 3 AEs), unsolicited AEs (including duration in case of grade 3 AEs), SAEs, intercurrent medical conditions, AEs leading to trial or vaccine withdrawal, AESIs and MAAEs experienced by the subject or any concomitant medications and vaccinations taken by the subject.

9.4.6 Visit 5 (Vaccination Dose 2 Rabipur®, Day 8)

The following procedures will be performed during Visit 5:

Group 1 only: Vaccination (Dose 2 Rabipur®):

- Review of criteria for vaccine delay (section 6.3).
- Urine pregnancy test for female subjects of childbearing potential.
- **Vaccination (Dose 2 Rabipur®)**.
- Post-injection vaccination site reactogenicity assessment after 1 hour and then subjects will be discharged if the vital signs are within normal ranges or have returned to pre-vaccination levels.
- Diary collection for solicited AEs occurring up to Day 8 (Dose 1 Rabipur®).
- Subjects will be issued with diary cards to record solicited AEs occurring on the day of vaccination (Dose 2 Rabipur®) and the following 7 days. Unsolicited AEs occurring on the day of vaccination up to Day 29 will also be recorded by the subject on the diary card. Subjects will be instructed on how to complete the diaries.

Groups 2-4 only:

- Diary review for solicited AEs occurring up to Day 8 (Dose 1 CV7202).
- Diary card returned to the subjects for collection of unsolicited AEs up to Day 29 (Dose 1 CV7202).

All subjects:

- Physical examination (including weight and general condition) and vital signs check (body temperature, pulse, blood pressure).
- Blood draw for:
  - Safety laboratory (~9 ml).
  - Immunogenicity – VNTs (~18 ml), IgM/IgG/IgA (~6 ml), PBMCs* for CMI (~40 ml), cytokine assessment (~6 ml [CV7202 groups only]), transcriptome profiling (~10 ml [CV7202 groups only]), immune receptor sequencing (~5 ml).

    * PBMCs will be taken for a subset of the first 5 subjects in Group 2 and all subjects in Groups 1, 3 and 4.
- Safety assessments (solicited AEs, unsolicited AEs, SAEs, intercurrent medical conditions, AEs leading to trial or vaccine withdrawal, AESIs and MAAEs, concomitant medications and vaccinations).

9.4.7 Visit 6 (Day 10)

The following procedures will be performed during Visit 6 for **Group 1 only**:

- Physical examination (including weight and general condition) and vital signs check (body temperature, pulse, blood pressure).
- Post-injection vaccination site reactogenicity assessment after 2 days in subjects having received Rabipur®dose 2.
- Diary card review and reminder.
- Safety assessments (solicited AEs, unsolicited AEs, SAEs, intercurrent medical conditions, AEs leading to trial or vaccine withdrawal, AESIs and MAAEs, concomitant medications and vaccinations).

9.4.8 Visit 7 (Day 15)

The following procedures will be performed during Visit 7:

- Physical examination (including weight and general condition) and vital signs check (body temperature, pulse, blood pressure).
- Diary card reminder/review for unsolicited AEs occurring up to Day 29 (Dose 1 CV7202).
- **Group 1 only:** Diary review for solicited AEs occurring up to Day 15 (Dose 2 Rabipur®).
- **Group 1 only:** Diary card returned to the subjects for collection of unsolicited AEs up to Day 36 (Dose 2 Rabipur®).
- Safety assessments (solicited AEs, unsolicited AEs, SAEs, intercurrent medical conditions, AEs leading to trial or vaccine withdrawal, AESIs and MAAEs, concomitant medications and vaccinations).
- Blood draw for:
  - Safety laboratory (~9 ml).

- Immunogenicity – VNTs (~18 ml), IgM/IgG/IgA (~6 ml).

9.4.9 Visit 8 (Vaccination Dose 2 CV7202* or Dose 3 Rabipur®, Day 29)

The following procedures will be performed during Visit 8:

- Review of criteria for vaccine delay (for Groups 1, 3a and 4a section 6.3).
- Urine pregnancy test for female subjects of childbearing potential.
- Physical examination (including weight and general condition) and vital signs check (body temperature, pulse, blood pressure).
- Blood draw for:
  - Safety laboratory (~9 ml).
  - Immunogenicity – VNTs (~18 ml), IgM/IgG/IgA (~6 ml) and immune receptor sequencing (~5 ml) in all subjects; cytokine assessment (~6 ml at pre-vaccination and ~6 ml at 4 hours post-vaccination [CV7202 groups only]) and transcriptome profiling (~10 ml at pre-vaccination [CV7202 groups only]) in subjects from Groups 3a and 4a who received a second dose of CV7202.

* The second dose will be administered to 8 subjects of each group (Groups 3a to 4a).

- **Vaccination (Dose 2 CV7202 or Dose 3 Rabipur®)**.
- Post-injection vaccination site reactogenicity assessment after 1 hour for all subjects who received a vaccine. Note that all subjects need to remain at the site for 4 hours after vaccination for safety monitoring. Vital signs will be then re-checked and have to be within normal ranges or have returned to pre-vaccination levels for the subject to be discharged.
- Diary review and collection for unsolicited AEs occurring up to Day 29 (Dose 1 CV7202 and Rabipur®) and up to Day 36 (Dose 2 Rabipur®).
- Subjects will be issued with diary cards to record solicited AEs occurring on the day of vaccination with Dose 2 CV7202 or Dose 3 Rabipur® and the following 7 days. Unsolicited AEs occurring on the day of vaccination and for the following 28 days will also be recorded by the subject on the diary card.
- Safety assessments (solicited AEs, unsolicited AEs, SAEs, intercurrent medical conditions, AEs leading to trial or vaccine withdrawal, AESIs and MAAEs, concomitant medications and vaccinations).

9.4.10 Visit 9 (Day 30 or 31**)

The following procedures will be performed during Visit 9 **only for Group 1 and subjects who received CV7202 Dose 2 (Groups 3a and 4a)**:

- Physical examination (including weight and general condition) and vital signs check (body temperature, pulse, blood pressure).
- Post-injection vaccination site reactogenicity assessment after 1 or 2 days* for all subjects who received Dose 2 CV7202 or Dose 3 Rabipur®.
- Diary card review and reminder.

- Safety assessments (solicited AEs, unsolicited AEs, SAEs, intercurrent medical conditions, AEs leading to trial or vaccine withdrawal, AESIs and MAAEs, concomitant medications and vaccinations).
- Blood draw for:
  - Safety laboratory (~9 ml)
  - Immunogenicity* – cytokine assessment (~6 ml), transcriptome profiling (~10 ml) only for CV7202 groups.

    * PBMCs will be taken for a subset of the first 5 subjects in Group 2 and all subjects in Groups 1, 3 and 4.

** For some subjects already vaccinated with Rabipur® before this protocol amendment was issued, Visit 9 occurred on Day 31 as planned in the original protocol. For other subjects, the visit should occur on Day 30.

9.4.11 Phone call (Day 31)

A phone call should be performed on Day 31 for the **CV7202 3a and 4a groups only** to collect the following safety information:

- Any solicited AEs (including duration in case of grade 3 AEs), unsolicited AEs (including duration in case of grade 3 AEs), SAEs, intercurrent medical conditions, AEs leading to trial or vaccine withdrawal, AESIs and MAAEs experienced by the subject or any concomitant medications and vaccinations taken by the subject.

9.4.12 Visit 10 (Day 36)

The following procedures will be performed during Visit 10:

- Physical examination (including weight and general condition) and vital signs check (body temperature, pulse, blood pressure).
- Diary review for solicited AEs occurring up to Day 36 (Dose 2 CV7202, Dose 3 Rabipur®).
- Diary card returned to the subjects for collection of unsolicited AEs up to Day 57 (Dose 2 CV7202, Dose 3 Rabipur®).
- Safety assessments (solicited AEs, unsolicited AEs, SAEs, intercurrent medical conditions, AEs leading to trial or vaccine withdrawal, AESIs and MAAEs, concomitant medications and vaccinations).
- Blood draw for:
  - Safety laboratory (~9 ml).
  - Immunogenicity – VNTs (~18 ml), IgM/IgG/IgA (~6 ml), PBMCs* for CMI (~40 ml) and immune receptor sequencing (~5 ml); cytokine assessment (~6 ml [CV7202 groups only]) and transcriptome profiling (~10 ml [CV7202 groups only]).

    * PBMCs will be taken for a subset of the first 5 subjects in Group 2 and all subjects in Groups 1, 3 and 4.

9.4.13 Visit 11 (Day 43)

The following procedures will be performed during Visit 11:

- Diary card review and reminder.
- Safety assessments (unsolicited AEs, SAEs, intercurrent medical conditions, AEs leading to trial or vaccine withdrawal, AESIs and MAAEs, concomitant medications and vaccinations).
- Blood draw for:
  - Immunogenicity – VNTs (~18 ml), IgM/IgG/IgA (~6 ml).

9.4.14 Visit 12 (Day 57)

The following procedures will be performed during Visit 12:

- Physical examination (including weight and general condition).
- Diary review and collection for unsolicited AEs occurring up to Day 57 (Dose 2 CV7202; Dose 3 Rabipur®).
- Safety assessments (unsolicited AEs, SAEs, intercurrent medical conditions, AEs leading to trial or vaccine withdrawal, AESIs and MAAEs, concomitant medications and vaccinations).
- Blood draw for:
  - Safety laboratory (~9 ml).
  - Immunogenicity – VNTs (~18 ml), IgM/IgG/IgA (~6 ml), immune receptor sequencing (~5 ml).

9.4.15 Visit 13 (Day 91)

The following procedures will be performed during Visit 13:

- Physical examination (including weight and general condition).
- Safety assessments (SAEs, intercurrent medical conditions, AEs leading to trial or vaccine withdrawal, AESIs and MAAEs, concomitant medications and vaccinations).
- Blood draw for:
  - Safety laboratory (~9 ml).
  - Immunogenicity – VNTs (~18 ml), IgM/IgG/IgA (~6 ml), PBMCs* for CMI (~40 ml), immune receptor sequencing (5 ml).

    * PBMCs will be taken for a subset of the first 5 subjects in Group 2 and all subjects in Groups 1, 3 and 4.

9.4.16 Visit 14 (Month 6: Day 181 [1-dose groups]/ Day 209 [2-dose groups and Group 1 (Rabipur®)]

9.4.16.1 Visit 14

The following procedures will be performed during Visit 14:

- Safety assessments (SAEs, intercurrent medical conditions, AEs leading to trial or vaccine withdrawal, AESIs and MAAEs, concomitant medications and vaccinations).
- Blood draw for:
  - Safety laboratory (~9 ml).
  - Immunogenicity – VNTs (~18 ml), IgM/IgG/IgA (~6 ml), PBMCs* for CMI (~40 ml), immune receptor sequencing (5 ml).

    * PBMCs will be taken for a subset of the first 5 subjects in Group 2 and all subjects in Groups 1, 3 and 4.

In case Visit 14 cannot take place on site due to the public health emergency related to COVID-19, safety information should be collected via a phone call within the protocol-allowed time interval for Visit 14 (±14 days).

9.4.16.2 Optional Visit 14A

Visit 14A may be conducted only in case Visit 14 was conducted as a phone call, and when restrictive measures related to COVID-19 no longer prevent site visits, and the window of Visit 14 has expired. Visit 14A allows the trial procedures, including the blood draws for safety and immunogenicity testing, to occur during a widened visit window starting the day after the expiry of the original visit window and lasting up to 3 months after the original projected visit date (+15-90 days). In that case, all procedures as described in Section 9.4.16.1 for Visit 14, including blood sampling for safety and immunogenicity assessments, should be performed at Visit 14A.

Also, in case Visit 14 was conducted on site but not all procedures could be performed, Visit 14A should be scheduled on site within the protocol-allowed time interval for Visit 14A (+15-90 days).

9.4.17 Visit 15 (Month 12: Day 365 [1-dose groups]/ Day 393 [2-dose groups and Group 1 (Rabipur®)]

9.4.17.1 Visit 15

The following activities will be performed during Visit 15:

- Physical examination (including weight, and general condition) and vital signs check (body temperature, pulse, blood pressure).
- Safety assessments (SAEs, intercurrent medical conditions, AEs leading to trial or vaccine withdrawal, AESIs and MAAEs, concomitant medications and vaccinations).
- Blood draw for:
  - Safety laboratory (~9 ml) (section 9.5.1).

- Immunogenicity – VNTs (~18 ml), IgM/IgG/IgA (~6 ml), PBMCs* for CMI (~40 ml), immune receptor sequencing (5 ml) (section 9.5.3).

  * PBMCs will be taken for a subset of the first 5 subjects in Group 2 and all subjects in Groups 1, 3 and 4.

In case Visit 15 cannot take place on site due to the public health emergency related to COVID-19, safety information should be collected via a phone call within the protocol-allowed time interval for Visit 15 (±30 days).

9.4.17.2 Optional Visit 15A

Visit 15A may be conducted only in case Visit 15 was conducted as a phone call, and when restrictive measures related to COVID-19 no longer prevent site visits, and the window of Visit 15 has expired. Visit 15A allows the trial procedures, including the blood draws for safety and immunogenicity testing, to occur during a widened visit window starting the day after the expiry of the original visit window and lasting up to 3 months after the original projected visit date (+31-90 days). In that case, all procedures as described in Section 9.4.17.1 for Visit 15, including and blood sampling for safety and immunogenicity assessments, should be performed at Visit 15A.

Also, in case Visit 15 was conducted on site but not all procedures could be performed, Visit 15A should be scheduled on site within the protocol-allowed time interval for Visit 15A (+31-90 days).

If no blood sampling could be performed at Visit 15 and 15A, the end-of-trial blood sample for safety assessment may be performed at Visit 17 (Month 24: Day 729).

9.4.18 Visit 16 (Month 18: Day 547)

9.4.18.1 Visit 16

The following activities will be performed during Visit 16:

- Safety assessments (SAEs related to study vaccination, MAAEs related to study vaccination, intercurrent medical conditions, AESIs and concomitant medications and vaccinations).
- Blood draw for immunogenicity (only in subjects with detectable RABV-G-specific IgG at 6 months after the last vaccination or Day 91 if the Month 6 blood sample is not available) – VNTs (~18 ml), IgG (~6 ml) (section 9.5.3).

In case Visit 16 cannot take place on site due to the public health emergency related to COVID-19, safety information should be collected via a phone call within the protocol-allowed time interval for Visit 16 (±30 days).

9.4.18.2 Optional Visit 16A

Visit 16A may be conducted only in case Visit 16 was conducted as a phone call, and when restrictive measures related to COVID-19 no longer prevent site visits, and the window of Visit 16 has expired. Visit 16A allows the trial procedures, including the blood draws for immunogenicity testing, to occur during a widened visit window starting the day after the expiry of the original visit window and lasting up to 3 months after the original projected visit date (+31-90 days). In that case, all procedures as described in

Section 9.4.16.1 for Visit 16, including blood sampling for immunogenicity assessment, should be performed at Visit 16A.

Also, in case Visit 16 was conducted on site but not all procedures could be performed, Visit 16A should be scheduled on site within the protocol-allowed time interval for Visit 16A (+31-90 days).

9.4.19 Visit 17 (Trial End) (Month 24: Day 729)

9.4.19.1 Visit 17

During the final trial visit, the following activities will be performed:

- Physical examination (including weight, and general condition) and vital signs check (body temperature, pulse, blood pressure).
- Safety assessments (SAEs related to study vaccination, MAAEs related to study vaccination, intercurrent medical conditions, AESIs and concomitant medications and vaccinations).
- Blood draw for immunogenicity (only in subjects with detectable RABV-G-specific IgG at 6 months after the last vaccination or Day 91 if the Month 6 blood sample is not available) – VNTs (~18 ml), IgG (~6 ml) (section 9.5.3).

If the subject withdraws prior to the end of the trial, trial end visit procedures should be performed.

Subjects should be asked whether they would agree to be contacted for participation in a follow-up trial.

In case Visit 17 cannot take place on site due to the public health emergency related to COVID-19, safety information should be collected via a phone call within the protocol-allowed time interval for Visit 17 (±30 days).

9.4.19.2 Optional Visit 17A

Visit 17A may be conducted only in case Visit 17 was conducted as a phone call, and when restrictive measures related to COVID-19 no longer prevent site visits, and the window of Visit 17 has expired. Visit 17A allows the trial procedures, including the blood draws for immunogenicity testing, to occur during a widened visit window starting the day after the expiry of the original visit window and lasting up to 6 months after the original projected visit date (+31-180 days). In that case, all procedures as described in Section 9.4.19.1 for Visit 17, including physical examination, measurement of vital signs and blood sampling for immunogenicity assessment, should be performed at Visit 17A.

Also, in case Visit 17 was conducted on site but not all procedures could be performed, Visit 17A should be scheduled on site within the protocol-allowed time interval for Visit 17A (+31-180 days).

If no blood sampling could be performed at Visits 15 and 15A, the end-of-trial blood sample for safety assessment may be performed at Visit 17 or 17A.

9.5 Blood Draws

Blood draws will occur at 16 visits and prior to vaccination (Visits 3, 5 and 8). In addition to the pre-vaccination blood sample at Visits 3 and 8, a blood sample at 4 hours post-vaccination will be taken for cytokine assessment in the CV7202 groups. Maximal volume taken per subject over the duration of the trial is ~809 ml (Table 9.3).

PBMCs will be taken for a subset of the first 5 subjects in Group 2 and all subjects in Groups 1, 3 and 4.

In case a site visit is not possible due to the public health emergency related to COVID-19, the blood sample for immunogenicity assessments at Months 6, 12, 18 and 24 should be performed at Visits 14A, 15A, 16A and 17A, respectively, only in case restrictive measures related to COVID-19 no longer prevent site visits (refer to Sections 9.4.16 to 9.4.19 for details).

Clinical laboratory tests are described in Appendix 6.

Table 9.3 Timing and Maximum Volumes of Blood Draws

Visit / Procedure	V1	V2	V3	V4	V5	V7	V8	V9	V10	V11	V12	V13	V14/ V14A§	V15/ V15A§	V16/ V16A§	V17/ V17A§	∑
Pregnancy Test (ml)*																	
Serum hCG	-	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	**2**
Safety (ml)																	
Safety Laboratory	-	9	9	9	9	9	9	9	9	-	9	9	9	9	-	-	**108**
TSH, Thyroid Antibodies, ANA	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	**3**
Immunogenicity (ml)																	
VNT	-	-	18	-	18	18	18	-	18	18	18	18	18	18	18‡	18‡	**216**
IgM/IgG/IgA	-	-	6	-	6	6	6	-	6	6	6	6	6	6	6‡	6‡	**72**
Cell-mediated Immunity	-	-	60	-	40	-	-	-	40	-	-	40	40	40	-	-	**260**
Cytokines**	-	-	12†	6	6	-	12†	6	6	-	-	-	-	-	-	-	**48**
Transcriptome Profiling**	-	-	10	10	10	-	10	10	10	-	-	-	-	-	-	-	**60**
Immune Receptor Sequencing	-	-	5	-	5	-	5	-	5	-	5	5	5	5	-	-	**40**
Total	**3**	**11**	**120**	**25**	**94**	**33**	**60**	**25**	**94**	**24**	**38**	**78**	**78**	**78**	**24**	**24**	**809**

∑ = Sum; No blood draw at Visit 6.

* For female subjects of childbearing potential.

** Cytokine and transcriptome profiling assessments will only be performed for subjects in the CV7202 groups.

§ The optional Visits 14A, 15A, 16A and 17A may only take place in case the respective visit could not be conducted as described in the protocol. If no blood sampling could be performed at Visits 15 and 15A, the end-of-trial blood sample for safety assessment may be performed at Visit 17.

† Two blood samples will be taken on the day of vaccination, i.e. at pre-vaccination and 4 hours post-vaccination.

‡ At Month 18 and Month 24, VNTs and IgG assessments will be performed only in subjects with detectable RABV-G-specific IgG at 6 months after the last vaccination or Day 91 if the Month 6 blood sample is not available.

9.5.1 Safety Lab (Visits 2 to 5, 7 to 10 and 12 to 15)

Safety laboratory assessments for hematology (complete blood count, including differential and platelets) and biochemistry will be performed as outlined in Appendix 6. Coagulation (activated partial thromboplastin time [aPTT]), and prothrombin time/international normalized ratio [INR]) will be performed at the following time points: Screening, Days 1, 3 and 31.

The approximate volume taken for safety laboratory is ~9 ml per visit. Blood will be taken for the safety laboratory at 12 visits.

In case a site visit is not possible due to the public health emergency related to COVID-19, the blood sample for safety assessment at Month 6 and Month 12 should be collected at Visit 14A and Visit 15A, respectively, only in case restrictive measures related to COVID-19 no longer prevent site visits (refer to Section 9.4.16 and 9.4.17 for details). If no blood sampling could be performed at Visits 15 and 15A (Month 12), the end-of-trial sample for safety assessment may be performed at Visit 17 (Month 24).

9.5.2 Thyroid-stimulating Hormone, Thyroid Antibodies, Antinuclear Antibodies (Pre-screening Visit)

The approximate volume taken for TSH, thyroid antibodies, ANA is ~3 ml per visit. Blood will be taken for TSH, thyroid antibodies, ANA at 1 visit. Blood drawn at the pre-screening visit will be kept for retrospective measurement of TSH, thyroid antibodies and ANA following the occurrence of clinical autoimmune events (other autoantibodies might be investigated as well depending on the clinical autoimmune event).

9.5.3 Immunogenicity (Visits 3 to 5, 7 to 17)

The approximate volumes taken for immunogenicity testing are:

- VNTs (serum) (~18 ml). Blood will be taken at 12 visits.
- IgM/ IgG ELISA (serum) (~6 ml). Blood will be taken at 12 visits.
- Cell-mediated immune response and leukocyte phenotyping of PBMCs (~60 ml at baseline and ~40 ml at subsequent visits) – PBMCs will be taken for the first 5 subjects in Group 2 and all subjects in Groups 3 and 4. In addition, all 10 subjects receiving Rabipur® will be included. Blood will be taken at 6 visits.
- Cytokine assessment (serum) (~6 ml) – for the subjects in the CV7202 groups providing PBMCs. A total of 7 (or 8 for subjects receiving 2 doses of CV7202) blood samples will be taken at 6 visits.
- Transcriptome profiling (PBMCs) (~10 ml) – for the subjects in the CV7202 groups providing PBMCs for cell-mediated immune response and leukocyte phenotyping. Blood will be taken at 6 visits.
- Immune receptor sequencing (PAXgene DNA) (~5 ml). Blood will be taken at 8 visits.

In case a site visit is not possible due to the public health emergency related to COVID-19, the blood sample for immunogenicity assessments should be collected at Visits A, only in case restrictive measures related to COVID-19 no longer prevent site visits (refer to Sections 9.4.16 to 9.4.19 for details).

10 Statistical Considerations

Due to the exploratory nature of this trial only descriptive statistics will be used, no confirmatory statistical inference will be performed.

10.1 Sample Size Determination

No statistically-based sample size estimation was performed.

10.2 Populations for Analyses

Safety set: This is the subset of subjects, who have received at least one dose of the candidate rabies mRNA vaccine CV7202 or the active control Rabipur® and for whom any post-Day 1 safety data are available. The statement that a subject had no AEs (on the Adverse Event eCRF) constitutes a valid safety assessment. The analysis of safety will be performed on this population.

Full-analysis (FA) set: This is the subset of the Safety Set with subjects who have the baseline sample and at least one additional blood sample available for VNT analysis. This analysis set is the primary analysis set for all immunogenicity objectives.

Per **protocol (PP) set**: This is defined as a subset of the FA set as follows:

1. PP1 = Subjects enrolled in Group 1 (Rabipur®) and Groups 2 to 4 who have received at least 1 administration of the trial product (including those to be selected for the second vaccination), have completed the Day 57 visit and for whom baseline through Day 57 immunological results (at least rabies VNTs) are available.
2. PP2 = Defined as a subset of PP1 comprised of subjects who have received two administrations of the trial product, have completed the Day 91 visit and for whom baseline through Day 91 immunological results (at least rabies VNTs) are available.

Any subject for whom substantive protocol deviations are documented will be excluded from the PP set. The following pre-defined major protocol deviations will lead to the exclusion from the PP set:

- Any deviation of the Inclusion/Exclusion criteria.
- Any trial subject that requires therapy listed as an exclusion criterion in section 6.2.
- Any trial subject that has not received the trial product on the scheduled date.
- Any trial subject for whom the immunological sample has been taken outside of the planned visit window.
- Pre-existing RABV-G specific immune response.

Further subgroup analyses may be defined and specified in the statistical analysis plan (SAP).

10.3 Statistical Analyses

10.3.1 General Considerations

All data obtained in this trial and documented in the eCRF will be listed and summarized with sample statistics or frequency tables as appropriate. In all tables, listings and figures the dose groups will be reported from the lowest to the highest dose, with the '**a**' groups as separate columns.

A statistical analysis plan (SAP) will be prepared and finalized at the latest prior to database lock for the interim analysis. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all trial objectives and the handling of missing data.

This trial is designed as an exploratory phase I trial with no confirmatory proof of hypotheses.

10.3.2 Demographic, Medical History, Prior Medication and other Baseline Characteristics

Demographic characteristics, medical history, prior medication and other baseline data will be listed and summarized using descriptive statistics for numerical data and contingency tables for categorical data. Medical history and prior medication will only be listed.

10.3.3 Study vaccine

The administrations of CV7202 will be listed.

10.3.4 Concomitant medication and Vaccinations

Concomitant medication/vaccination and significant non-drug therapies after the start of study treatment will be listed and summarized by Anatomical Therapeutic Chemical (ATC) term in contingency tables.

10.3.5 Safety Analyses

The following safety and reactogenicity data will be summarized descriptively: vital signs, and vaccination site reactogenicity assessment.

The occurrence of solicited local and systemic AEs reported on the day of each vaccination and the 7 subsequent days and unsolicited AEs reported on the day of each vaccination and the 28 subsequent days will be presented.

The safety measurements will include:

1. AEs (type, intensity, frequency and relationship to vaccination), i.e. incidence and severity of AEs for both solicited local and systemic events (occurring on the day of vaccination and the 7 subsequent days) and unsolicited events (occurring on the day of vaccination and the 28 subsequent days).
2. SAEs, MAAEs and AEs leading to trial or vaccine withdrawal up to 12 months post last dose. After Visit 15 (Month 12), only SAEs and MAAEs that according to the

investigator are considered to be related to study vaccination will be collected.

3. Intercurrent medical conditions and AESIs throughout the trial.
4. Local reactogenicity assessment of injection site in all subjects.

Further, the incidence of AEs will be summarized in frequency tables by Medical Dictionary for Regulatory Activities (MedDRA) terms (system organ class [SOC] and preferred term [PT]). AEs that are reported as related to the test vaccine will be considered trial vaccine-related; missing classifications concerning trial vaccine relationship will also be considered trial vaccine-related.

Concomitant medications and vaccinations will be coded and summarized. Physical examination data will be listed.

Clinical laboratory test results with values below/above the reference range will be counted.

10.3.6 Immunogenicity Analyses (Secondary/Exploratory Objectives)

Baseline is defined as Day 1 (Visit 3; before vaccination).

Immune response will be assessed using the following parameters:

1. Number and percentage of subjects having VNTs ≥0.5 IU/ml on Days 1, 15, 43, and 12, 18 and 24 months post last dose.
2. Individual functional antibody titers, GMTs and range of titers in sera collected on Days 1, 8, 15, 29, 36, 43, 57, 91, and 6, 12, 18 and 24 months post-last dose.

Further immunogenicity assessments will be based on VNTs, RABV-G-specific IgG, IgM and IgA serum antibodies, RABV-G-specific T cells and B cells in peripheral blood and other immunogenicity-related parameters such as cytokine serum concentrations, including but not limited to CXCL10, CCL3, IL-6, TNF -α and IFN-γ, gene expression changes, antibody affinity and avidity, throughout the duration of the trial. Results will be summarized in tables, figures and supported by subject level listings.

10.3.7 Missing data

Analysis of vaccination variables will be done on a valid case basis, i.e., for missing observations, no imputation for missing data, such as last observation carried forward (LOCF), will be applied. For safety data, some missing or partially missing variables will be imputed as follows:

- For start date:
  - If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to missing.
  - If the AE start date year value is less than the treatment start date year value, the AE started before treatment. Therefore:
    - If the AE year is lower than the treatment year and the AE month is missing, the imputed AE start date is set to the mid-year point (i.e., 01JULYYYY).

    - If the AE year is lower than the treatment year and the AE month is not missing, the imputed AE start date is set to the mid-month point (i.e., 15MONYYYY).
  - If the AE start date year value is greater than the treatment start date year value, the AE started after treatment. Therefore, if the AE year is greater than the treatment year and the AE month is missing, the imputed AE start date is set to the year start point (i.e., 01JANYYYY).
- For resolution date:
  - If date of resolution is completely missing, it is assumed that it resolved at the date of the end of the AE assessment period.
  - If year is present, it is assumed that it resolved on 31 December of that year (i.e., 31DECYYYY), or at the end of the AE assessment period if earlier.
  - If year and month are present, it is assumed that it resolved on the last day of that month, or at the end of the AE assessment period if earlier.

No other safety variables will be imputed. In case the number of missing/partial dates for solicited local AEs, solicited systemic AEs or individual solicited AEs is higher than expected for the analysis of durations (in days), a sensitivity analysis will be conducted to assess the impact on the primary endpoint.

10.3.8 Interim analyses

One or more interim analyses may be performed for this trial. The data will be cleaned for all subjects. The analyses will be based on a data snapshot. Analyses will be performed on the safety set only. No decision-making is planned for the interim analyses and no adjustments for the trial are planned based on the results. As this trial is of exploratory nature and no inferential statistics are planned, no adjustment for multiple testing will be done.

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12 Appendices

The following appendices are provided below:

Appendix 1 Investigator Signature Page

Protocol Title: A non-randomized, open label, controlled, dose-escalation, phase I clinical trial to evaluate the safety, reactogenicity and immunogenicity of one or two administrations candidate rabies mRNA vaccine CV7202 in healthy adult subjects

Protocol Number: CV-7202-104

Confidentiality and GCP Compliance Statement

I, the undersigned, have reviewed this protocol, including appendices and I will conduct the trial as described in compliance with this protocol, GCP, and relevant ICH guidelines.

I understand that all information obtained during the conduct of the trial with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all eCRFs and laboratory samples. Clinical information may be reviewed by the sponsor or designee or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.

Institution

Protocol Title: A non-randomized, open label, controlled, dose-escalation, phase I clinical trial to evaluate the safety, reactogenicity and immunogenicity of one or two administrations candidate rabies mRNA vaccine CV7202 in healthy adult subjects

Protocol Number: CV-7202-104

Confidentiality and GCP Compliance Statement

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I understand that all information obtained during the conduct of the trial with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all eCRFs and laboratory samples. Clinical information may be reviewed by the sponsor or designee or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.

Appendix 2 Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations.

The investigator agrees to assume the following responsibilities:

1. Conduct the trial in accordance with the protocol ICH-E6 (R2), and all the applicable local laws and regulations.
2. Personally conduct or supervise the staff who will assist with the protocol.
3. Ensure that trial related procedures including trial specific (non-routine/non-standard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the trial are informed of these obligations.
5. Secure prior approval of the trial and any changes by an appropriate IEC and competent authority.
6. Ensure that the IEC will be responsible for initial review, continuing review, and approval of the protocol.
7. Ensure that requirements for informed consent, as outlined in ICH-E6 (R2) 4.8 and local regulations, are met.
8. Obtain valid informed consent from each subject and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the trial. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject.
9. Prepare and maintain adequate case histories of all persons entered into the trial, including eCRFs, hospital records, laboratory results, etc., and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Ensure that clinical data is entered into the eCRFs within 24 hours of the visit day during the staggered enrolment phase and within 5 days post-visit for all other visits. In case a subject forgets to bring the diary card to a review visit, the subject will be requested to provide a fax-copy, photo-copy or scan of the diary to the site staff as soon as possible after the visit.
11. Allow possible inspection and copying by the regulatory authority of GCP-specified source documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied vaccines, and return all unused sponsor-supplied vaccines to the sponsor.

13. In the event of an SAE, AESI or overdose notify [redacted] within 24 hours via SAE/AESI/overdose report form signed by the investigator.
14. Review and provide a signature as approval of the content of the clinical study report.

Appendix 3 Protocol Approvers

Protocol Title: A non-randomized, open label, controlled, dose-escalation, phase I clinical trial to evaluate the safety, reactogenicity and immunogenicity of one or two administrations of candidate rabies mRNA vaccine CV7202 in healthy adult subjects

Protocol Number: CV-7202-104

Protocol Approvers

Appendix 4 Emergency Procedures

During and after subjects' participation in this trial, the investigator or institution should ensure that adequate medical care is provided to subjects who present with any AEs, including clinically significant laboratory values related to the administration of trial IMP. The investigator or institution should inform subjects when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

Emergency equipment for the immediate treatment of allergic/anaphylactic reactions (steroids, H1, H2 antihistaminergic agents, intravenous fluids, oxygen, epinephrine and equipment for cardiopulmonary resuscitation) must be available at all times for the treatment of these events, and trained personnel must be present at all times while subjects are being monitored after vaccination.

The trial site should have immediate access to equipment and appropriately qualified staff for resuscitating and stabilizing subjects in an acute emergency (such as cardiac emergencies, anaphylaxis, cytokine release syndrome, convulsions, hypotension), and ready availability of intensive care unit and other hospital facilities.

Appendix 5 Abbreviations and Trademarks

AE	Adverse event
AESI	Adverse event of special interest
ANA	Antinuclear antibody
API	Active Pharmaceutical Ingredient
aPTT	Activated partial thromboplastin time
BCR	B-cell receptor
CA	Competent authorities
CCL	Chemokine (CC motif) ligand
CDC	Centers for Disease Control and Prevention (US)
CMI	Cell-mediated immunity
CRO	Contract research organization
CXCL	Chemokine (C-X-C motif) ligand
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
ELISA	Enzyme-linked immunosorbent assay
FA	Full analysis
FDA	US Food and Drug Administration
FIH	First-in-human
GCP	Good Clinical Practice
GMT	Geometric mean titer
hCG	Human chorionic gonadotropin
IB	Investigator's brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
i.d.	Intradermal
IEC	Independent Ethics Committee
IFN-γ	Interferon-gamma
Ig	Immunoglobulin
IL	Interleukin
i.m.	Intramuscular
IMP	Investigational medicinal product
INR	International normalized ratio
iSRC	Internal safety review committee
IUD	Intrauterine device
IUS	Intrauterine systems
LNP	Lipid nanoparticles
MAAE	Medically-attended adverse event
mRNA	Messenger ribonucleic acid
NHP	Non-human primate
NOAEL	No-observed-adverse-effect level
PBMC	Peripheral blood mononuclear cell
PI	Principal Investigator
pIMD	potential Immune Mediated Disease
PP	Per protocol
RABV-G	Rabies virus glycoprotein

RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SOP	Standard operating procedure
TNF-α	Tumor necrosis factor-alpha
TSH	Thyroid stimulating hormone
VNT	Virus-neutralizing antibody titer
WHO	World Health Organization

Appendix 6 Clinical Laboratory Tests

The tests detailed in Table 12.1 will be performed by the local laboratory.

Additional tests may be performed at any time during the trial as determined necessary by the investigator or required by local regulations.

Table 12.1 Protocol-Required Safety Laboratory Assessments

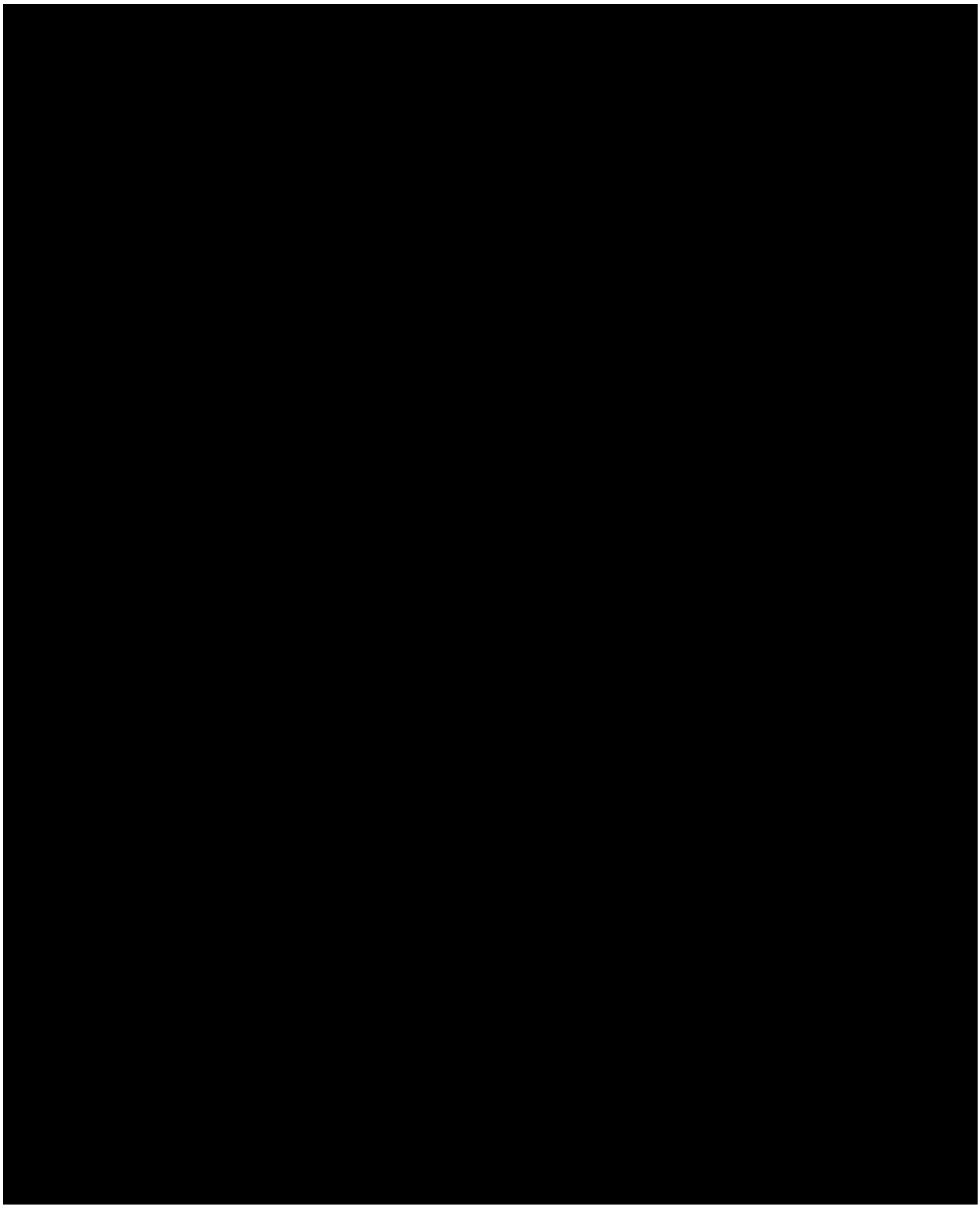
Laboratory Assessments	Parameters
Hematology	Complete blood count including differential and platelets
Biochemistry	Magnesium, creatinine, albumin and lactate dehydrogenase (LDH), C-reactive protein (CRP), gamma glutamyl transferase (GGT), blood urea nitrogen (BUN), bilirubin, calcium, alkaline phosphatase, sodium, potassium, total protein, glutamic oxaloacetic transaminase (GOT)/ aspartate aminotransferase (ASAT), glutamic pyruvic transaminase (GPT)/alanine aminotransferase (ALAT)
Coagulation	Prothrombin time/international normalized ratio (INR), activated partial thromboplastin time (aPTT)
Serum Pregnancy Tests	Human chorionic gonadotropin (hCG)

The investigator must document his review of each laboratory safety report, by signing and dating the report.

Appendix 7 Trial Governance Considerations

CureVac AG is the sponsor of this trial. A contract research organization (CRO) will organize the performance of this trial.

Table 12.2 List of Names and Addresses



Appendix 8 Protocol changes

Amendments to this trial protocol may be made following the procedures specified by local laws and regulations. Substantial amendments to this trial protocol may be implemented only if the approval of the competent authority / authorities [CA(s)] and a favorable opinion of the Independent Ethics Committee(s) [IEC(s)] have been obtained.

Substantial amendments to the conduct of the clinical trial may arise from changes to the protocol or from new information relating to the scientific documents in support of the trial. Amendments to the trial are regarded as “substantial” where they are likely to have a significant impact on:

- The safety, physical health and mental integrity of the subjects.
- The scientific value of the trial.
- The conduct or management of the trial.
- The quality or safety of any IMP used in the trial.

If a new event occurs related to the conduct of the trial or the development of the investigational medicinal product, which may affect the safety of the subjects, the sponsor and the investigator will take appropriate safety measures to protect the subjects against any immediate hazard. The sponsor will immediately inform the CA(s) and IEC(s) of the new events and the measures taken.

Appendix 9 Disclosure

Publication of results

The original data and the data otherwise obtained during the trial under this trial protocol will become the property of the sponsor. Any publication or scientific communication related to this trial can only take place once the manuscript has been reviewed by the sponsor, and once a written agreement between the sponsor and the investigator has been reached.

The sponsor will follow all applicable regulations and legal obligations in regards to disclosure of data.

Clinical trial report

After completion of the trial, the results will be tabulated, evaluated and issued as a complete final clinical trial report according to the ICH-E3 Note for guidance on structure and content of clinical trial reports.

The sponsor will send a summary of this clinical trial report to the EC and CA within 1 year after the end of the trial defined as the last subject's last follow up visit.

Appendix 10 Adverse Events of Special Interest

Current list of AESIs

Gastrointestinal disorders:
- o Celiac disease
- o Crohn's disease
- o Ulcerative colitis
- o Ulcerative proctitis

Liver disorders:
- o Autoimmune cholangitis
- o Autoimmune hepatitis
- o Primary biliary cirrhosis
- o Primary sclerosing cholangitis

Metabolic diseases:
- o Addison's disease
- o Autoimmune thyroiditis (including Hashimoto thyroiditis)
- o Diabetes mellitus type I
- o Grave's or Basedow's disease

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

Neuro-inflammatory disorders:
- o Acute disseminated encephalomyelitis, including site specific variants (e.g., non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculomyelitis)
- o Cranial nerve disorders, including paralyses/paresis (e.g., Bell's palsy)
- o Guillain-Barré syndrome, including Miller Fisher syndrome and other variants
- o Immune-mediated peripheral neuropathies and plexopathies, including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy
- o Multiple sclerosis
- o Narcolepsy
- o Optic neuritis
- o Transverse Myelitis

Current list of AESIs (cont.)

Skin disorders:

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

Vasculitides:

- o Large vessels vasculitis including: giant cell arteritis such as Takayasu's arteritis and temporal arteritis
- o Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg-Strauss syndrome (allergic granulomatous angiitis), Buerger's disease thromboangiitis obliterans, necrotizing vasculitis and anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), Henoch- Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis

Others:

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

Appendix 11 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of an AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. • An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • All AEs fall into one of two categories: “non-serious” or “serious”.
Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to a known concomitant disease). • Exacerbation of a pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after trial vaccine administration even though it may have been present before the start of the trial. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either trial vaccine, including Rabipur® or a concomitant medication/vaccination. • An adverse effect of the trial vaccine, including Rabipur® or concomitant medication/vaccination. • An accident or injury.
Events <u>NOT</u> Meeting the AE Definition
• Surgical procedures or other therapeutic interventions themselves are not AEs, but the condition for which the surgery/intervention is required is an AE and should be documented accordingly. • Planned surgical measures and the condition(s) leading to these measures are not AEs, if the condition(s) was (were) known before the period of observation (see below) and did not worsen during study. In the latter case the condition should be reported as medical history. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

• Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the trial that do not worsen.

Definition of an SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:
• Results in death.
• Is life-threatening. The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
• Requires inpatient hospitalization or prolongation of existing hospitalization: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
• Results in persistent disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
• Is a congenital anomaly/birth defect in the offspring of the subject.
• Is an important medical event: Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or

convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- SAEs need to be reported to [redacted] within 24 hours (see section Reporting of SAEs).
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to [redacted] in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by [redacted]. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to [redacted].
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- AESIs and cases of overdose must be documented and medically assessed by the investigator and the outcome described on the SAE/AESI/overdose report form.
- Pregnancy must be documented and medically assessed by the investigator and the outcome described on the Pregnancy Report Form which is to be sent to [redacted].

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the trial and assign it to 1 of the following categories [25]:

- **Absent.**
- **Mild**: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- **Moderate**: An event that causes sufficient discomfort to interfere with normal everyday activities.
- **Severe**: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between trial vaccine and each occurrence of each AE/SAE. Causality will be determined as:

- Related: There is a reasonable causal relationship between the IMP and the AE.
- Unrelated: There is no reasonable causal relationship between the IMP and the AE.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy or vaccination, and other risk factors, as well as the temporal relationship of the event to trial vaccine administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information for Rabipur® [24], in his assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to [redacted] However, **it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to [redacted].**
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- All local solicited symptoms are considered related to vaccination.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by [redacted] to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject dies during participation in the trial or during the follow-up period, the investigator will provide [redacted] with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to [redacted] within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting to [redacted] via Paper CRF
• Email or facsimile transmission of the SAE/AESI/overdose paper report form is the preferred method to transmit this information to [redacted]/medical monitor or the SAE coordinator. The investigator will document the date when any employee/co-investigator had first been aware of the report and fax or e-mail all SAE reports (initial and follow-up reports) even if they are incomplete within 24 hours upon receipt to [redacted]: [redacted] • In rare circumstances and in the absence of email or facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE report form within the designated reporting time frames. • The "**initial SAE report**" should be as complete as possible, including causality assessment, details of the current illness and (S)AE, the reason why the event was considered serious; date of onset and end date (if applicable); diagnostic procedures and treatment of the event; relevant medical history and concomitant medication and vaccinations; and action taken with trial vaccine. The SAE report form must be signed by the investigator or his authorized designee(s). • Investigator must inform [redacted] about AESIs and cases of overdose by applying the same timelines and rules of SAEs reporting.
Determination of Expectedness, Reference Safety Information
• Expectedness will be determined by [redacted] according to the designated Reference Safety Information (RSI) provided in the current IB. Any updates or substantial amendments will be considered accordingly.
Observation Period
• For the purpose of this trial, the period of observation for collection of AEs extends from the time the subject gives informed consent until the end of the trial. • All AEs that occur in the course of the clinical trial regardless of the causal relationship should be monitored and followed up until the outcome is known or it is evident that no further information can be obtained. • There must be documented reasonable attempts to obtain follow-up information and outcome. • It is the responsibility of the investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

Post-Trial Events
• If the investigator becomes aware of any SAE that occurred after the end of the trial but is considered to be caused by the trial vaccine(s), this must be reported to [redacted]. • These SAEs will be processed by [redacted]. Instructions for how to submit these SAEs will be provided in a handout in the Investigator Site File.

Appendix 12 Contraceptive Guidance and Collection of Pregnancy Information

Contraceptive Guidance

Females of childbearing potential must use acceptable methods of birth control from 2 weeks before the first administration of the test vaccine until 3 months following the last administration. The following methods of birth control are acceptable when used consistently and correctly:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal);
- progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable);
- intrauterine devices (IUDs);
- intrauterine hormone-releasing systems (IUSs);
- bilateral tubal occlusion;
- vasectomized partner;
- sexual abstinence (periodic abstinence [e.g., calendar, ovulation, symptothermal and post-ovulation methods] and withdrawal are not acceptable).

Males must use reliable forms of contraception (condom) from the moment of the first administration of the test vaccine until 3 months following the last administration and must refrain from sperm donation from the moment of the first administration of the test vaccine until 3 months after the last administration.

Refer to the Clinical Trial Facilitation Group (CTFG) recommendations on contraception and pregnancy testing for further details [23].

Reporting and Follow-up of pregnancies

Pregnancy is an exclusion criterion for enrolment in this trial, but subjects could potentially become pregnant during their active participation in this trial.

Any pregnancy in a subject having received a trial vaccine must be reported to [redacted] within 24 hours of the site learning of its occurrence, using a pregnancy reporting form. If the subject becomes pregnant during the trial, she will not receive any further doses of any sponsor-supplied trial vaccine. The pregnancy must be followed to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if the intended duration of safety follow-up for the trial has ended.

The trial site should maintain contact with pregnant subjects to obtain pregnancy outcome information.

Any complications during pregnancy (e.g., gestational diabetes or eclampsia) are to be considered as an AE; however, these complications could result in the event being an SAE. Spontaneous abortions, fetal death, stillbirth and congenital anomalies reported in the baby are always considered as SAEs. The pregnancy by itself will not be processed as an SAE. The investigator will follow the subject until completion of the pregnancy and must assess the outcome in the shortest possible time but not

more than 30 days within completion of the pregnancy. The investigator should notify [redacted] of the outcome of the pregnancy by submitting a Follow-up Pregnancy Report.

Appendix 13 Data Management and Quality Control

Case report forms

In this study, all clinical data (including, but not limited to, AE/SAEs, concomitant medications/vaccines, medical history, and physical assessments) will be entered onto eCRFs in a timely fashion (on the visit day during the staggered enrolment phase and within 5 days post-visit for all other visits) by the investigator and/or the investigator's dedicated site staff. All data entered into the eCRF must be verifiable against source documents at the trial site. Any changes to the data entered into the electronic data capture system will be recorded in the audit trail.

The investigator will maintain adequate and accurate records for each subject entered into the trial. Source documents such as hospital, clinic or office charts, laboratory reports, trial worksheets, and signed informed consent documents are to be included in the investigator's files along with subject trial records.

The sponsor or the CRO will check eCRF entries against source documents according to the guidelines of GCP. The consent form will include a statement by which subjects allow the sponsor or designee, as well as authorized regulatory agencies, to have direct access to source data that support data of the eCRF (e.g., subject medical files, appointment books, original laboratory records, etc.). The sponsor or designee, bound by secrecy, will not disclose subject identities or personal medical information.

Quality control

A monitor from the CRO will supervise the trial. The trial monitor will contact the investigator regularly to discuss the progress of the trial and to check the trial documents including the informed consent forms for completeness and consistency.

The trial monitor or representative of the sponsor will cross-check the data entered in the eCRF with the source data at the trial site in order to verify adherence to the trial protocol.

The eCRF will be checked for completeness and correctness by the monitor and data management department of the CRO according to the CRO's standard operating procedures (SOPs). The investigator will resolve any queries.

Trial site monitoring visits

Monitoring visits to the trial site will be made periodically during the trial to ensure that:

- The rights and well-being of human subjects are protected
- The reported study data are accurate, complete and verifiable from the source documents and
- The conduct of the trial is in compliance with the current approved protocol/amendment(s), GCP and applicable regulatory requirements.

The investigator and/or trial staff must make source documents for subjects enrolled in this trial available for inspection by CureVac AG or its designee at the time of each monitoring visit and sponsor audits, when applicable. These documents must also be

available for inspection, verification and copying, as required by regulators, by officials of the regulatory health authorities and/or IECs.

All aspects of the trial and its documentation will be subject to review by the sponsor or designee, including but not limited to the Investigator's Site File, trial vaccine, pharmacy records, subject medical records, informed consent documentation, and review of eCRFs and associated source documents. It is important that the investigator and other trial personnel are available during the monitoring visits and that sufficient time is devoted to the process.

Audits

The trial site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the vaccine is stored and prepared, and any other facility used during the trial. In addition, there is the possibility that this trial may be inspected by regulatory agencies, including those of local (EU-EMA) or foreign governments (e.g. US-FDA and others). If the trial site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee direct access for quality assurance auditors and inspectors to all trial documents and source data.

Appendix 14 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to trial subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the Responsible Medical Monitor (and Independent Ethics Committee [IEC], as required) to determine the appropriate course of action.

Protocol deviations due to COVID-19 illness and/or control measures should be documented with the reason for the deviation.

Appendix 15 Ethics and Regulations

Independent ethics committees and competent authorities

The clinical trial authorization granted by the competent authority (CA) and a favorable opinion from the relevant IEC(s) will be obtained prior to the start of the trial. The local authorities will be notified about the trial as required by law.

The CA and the IEC will be notified about the end of the trial and a report summarizing the trial results will be sent to the CA and the IEC within 1 year after the end of the trial. If the trial is terminated early, the CA and the IEC will be notified within 15 days.

Ethical conduct of the trial

The trial will be conducted in accordance with the ethical principles set forth in the Declaration of Helsinki (including amendments).

Subject information and consent

Written informed consent will be obtained from all subjects prior to entry into the trial. The investigator will explain to each subject orally and in writing (subject information sheet) the nature, significance, risks and implications of the trial before inclusion. In particular, the subjects will be informed about the following:

- The possibility of withdrawing from the clinical trial at any time by revoking the consent and without any resulting disadvantage.
- How personal and health-related data will be collected and used during the trial.

All subjects will receive a copy of the subject information sheet and a copy of their signed and dated informed consent form.

All subjects will be insured against injury caused by their participation in the trial according to legal requirements. They will be informed about the insurance and the resulting obligations on their part.

Legal and regulatory requirements

This trial will be carried out in accordance with GCP as required by European Union (EU) Directive 2001/20/EC and the relevant laws and regulations of the country in which the trial takes place.

Insurance policy

The sponsor will obtain liability insurance covering his and the investigator’s responsibility as well as the responsibility of any person involved in the conduct of the trial, provided there is proper adherence to the protocol. An insurance certificate will be provided by the sponsor to the IEC, if required.

Appendix 16 Biological Samples and Record Retention

Biological Samples Retention and Destruction

Collected specimens (blood) will be processed, stored and frozen appropriately for analysis. The sponsor has put into place a system to protect subjects' personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction. Excess biological specimens may be further tested with regard to investigation of the vaccine effect.

Retention of trial records

Records and source documents pertaining to the conduct of the trial and the distribution of the investigational medicinal product (e.g., informed consent forms [ICFs], laboratory slips, vaccination inventory records, and other pertinent information) must be retained by the investigator for a period of at least 15 years.