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Supplementary appendix

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Appendix

Supplement to:
Kremsner PG, et al. Efficacy and safety of the CVnCoV SARS-CoV-2 mRNA vaccine candidate: results from HERALD, a phase 2b/3, randomised, observer-blinded, placebo-controlled clinical trial in ten countries in Europe and Latin America. *Lancet Infectious Diseases*…

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Criteria for study participation

Inclusion criteria

Participants were enrolled in this trial only if they met all of the following criteria:

1. Male or female participants 18 years of age or older.
2. Willing and able to provide written informed consent prior to initiation of any trial procedures.
3. Expected compliance with protocol procedures and availability for clinical follow-up through the last planned visit.
4. Females of non-childbearing potential, defined as follows:
   surgically sterile (history of bilateral tubal ligation/occlusion, bilateral oophorectomy or hysterectomy) or postmenopausal (defined as amenorrhea for ≥ 12 consecutive months prior to screening (Day 1) without an alternative medical cause).
   A follicle-stimulating hormone (FSH) level may be measured at the discretion of the Investigator to confirm postmenopausal status.
5. Females of childbearing potential: negative pregnancy test {human chorionic gonatropin {hCG)} within 24 hours prior to each trial vaccination on Day 1 and Day 29.
6. Females of childbearing potential must use highly effective methods of birth control from 2 weeks before the first administration of the trial vaccine until 3 months following the last administration.
   The following methods of birth control are considered highly effective when used consistently and correctly:
   - Combined (oestrogen 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 ligation;
   - Vasectomized partner or infertile partner;
   - Sexual abstinence, periodic abstinence (e.g., calendar, ovulation, symptothermal and post-ovulation methods) and withdrawal are not acceptable.

Exclusion criteria

Participants were not enrolled in this trial if they met any of the following criteria:

1. History of virologically-confirmed COVID-19 illness.
2. For females: pregnancy or lactation.
3. Use of any investigational or non-registered product (vaccine or drug) within 28 days preceding the administration of the first trial vaccine or planned use during the trial.
4. Receipt of licensed vaccines within 28 days (for live vaccines) or 14 days (for inactivated or any other vaccines) prior to the administration of the first trial vaccine.
5. Prior administration of any investigational SARS-CoV-2 vaccine or another coronavirus (SARS-CoV, MERS-CoV) vaccine or planned use during the trial.
6. Any treatment with immunosuppressants or other immune-modifying drugs (including but not limited to anabolic steroids, corticosteroids, biologicals and methotrexate) for > 14 days total within 6 months preceding the administration of trial vaccine or planned use during the trial. For corticosteroid use, this means prednisone or equivalent, 0.5 mg/kg/day for 14 days or more. The use of inhaled, topical, or localized injections of corticosteroids (e.g., for joint pain/inflammation) is permitted.
7. Any medically diagnosed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination including known infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV); current diagnosis of or treatment for cancer including leukaemia, lymphoma, Hodgkin disease, multiple myeloma, or generalized malignancy; chronic renal failure or nephrotic syndrome; and receipt of an organ or bone marrow transplant.
8. History of angioedema (hereditary or idiopathic) or history of any anaphylactic reaction.
9. History of pIMD.
10. History of allergy to any component of CVnCoV vaccine.
11. Administration of immunoglobulins or any blood products within 3 months prior to the administration of trial vaccine or planned receipt during the trial.
12. Participants with a significant acute or chronic medical or psychiatric illness that, in the opinion of the Investigator, precludes trial participation (e.g., may increase the risk of trial participation, render the participant unable to meet the requirements of the trial, or may interfere with the participant's trial

evaluations). These include severe and/or uncontrolled cardiovascular disease, gastrointestinal disease, liver disease, renal disease, respiratory disease, endocrine disorder, and neurological and psychiatric illnesses. However, those with controlled and stable cases can be included in the trial.

13. Participants with impaired coagulation or any bleeding disorder in whom an intramuscular injection or a blood draw is contraindicated.
14. Foreseeable non-compliance with the trial procedures as judged by the Investigator.

Table S1 Severity of solicited local reactions

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

Adapted from U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research. Guidance for Industry – Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. September 2007

Table S2 Severity of solicited systemic reactions

Adapted from U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research. Guidance for Industry – Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. September 2007

	Grade 0	Grade 1	Grade 2	Grade 3
Fever	< 38·0 °C	≥38·0 – 38·4°C	≥38·5 – 38·9°C	≥39·0°C
Headache	Absent	Mild, no interference with normal activity	Moderate, some interference with normal activity and/or repeated use of non-narcotic pain reliever > 24 hours	Significant; any use of narcotic pain reliever and/or prevents daily activity
Fatigue	Absent	Mild, no interference with normal activity	Moderate, some interference with normal activity	Significant, prevents normal activity
Chills	Absent	Mild, no interference with normal activity	Moderate, some interference with normal activity	Significant, prevents normal activity
Myalgia	Absent	Mild, no interference with normal activity	Moderate, some interference with normal activity	Significant, prevents normal activity
Arthralgia	Absent	Mild, no interference with normal activity	Moderate, some interference with normal activity	Significant, prevents normal activity
Nausea/vomiting	Absent	Mild, no interference with normal activity and/or 1 – 2 episodes/ 24 hours	Moderate, some interference with activity and/or >2 episodes/ 24 hours	Significant, prevents daily activity, requires outpatient IV hydration
Diarrhoea	Absent	2 – 3 loose stools over 24 hours	4 – 5 stools over 24 hours	6 or more watery stools over 24 hours or requires outpatient IV hydration

Table S3 Adverse events of special interest – potential immune-mediated diseases

Gastrointestinal disorders:	**Neuro-inflammatory disorders:**
• Celiac disease • Crohn's disease • Ulcerative colitis • Ulcerative proctitis	• Acute disseminated encephalomyelitis, including site specific variants (e.g., non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculomyelitis) • Cranial nerve disorders, including paralyses/paresis (e.g., Bell's palsy) • Guillain-Barré syndrome, including Miller Fisher syndrome and other variants • Immune-mediated peripheral neuropathies, Parsonage-Turner syndrome and plexopathies, including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, and polyneuropathies associated with monoclonal gammopathy • Multiple sclerosis • Narcolepsy • Optic neuritis • Transverse Myelitis
Liver disorders:	
• Autoimmune cholangitis • Autoimmune hepatitis • Primary biliary cirrhosis • Primary sclerosing cholangitis	
Metabolic diseases:	
• Addison's disease • Autoimmune thyroiditis (including Hashimotthyroiditis) • Diabetes mellitus type I • Grave's or Basedow's disease	
Skin disorders:	**Vasculitides:**
• Alopecia areata • Autoimmune bullous skin diseases, including pemphigus, pemphigoid and dermatitis herpetiformis • Cutaneous lupus erythematosus • Erythema nodosum • Morphoea • Lichen planus • Psoriasis • Sweet's syndrome • Vitiligo	• Large vessels vasculitis including: giant cell arteritis such as Takayasu's arteritis and temporal arteritis • 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
Musculoskeletal disorders:	**Others:**
• Antisynthetase syndrome • Dermatomyositis • Juvenile chronic arthritis (including Still's disease) • Mixed connective tissue disorder • Polymyalgia rheumatic • Polymyositis • Psoriatic arthropathy • Relapsing polychondritis • Rheumatoid arthritis • Scleroderma, including diffuse systemic form and CREST syndrome • Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis • Systemic lupus erythematosus • Systemic sclerosis	• Antiphospholipid syndrome • Autoimmune haemolytic anaemia • Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis • Rapidly progressive, membranous glomerulonephritis, membranoproliferative • Glomerulonephritis, and mesangioproliferative glomerulonephritis) • Autoimmune myocarditis/cardiomyopathy • Autoimmune thrombocytopenia • Goodpasture syndrome • Idiopathic pulmonary fibrosis • Pernicious anaemia • Raynaud's phenomenon • Sarcoidosis • Sjögren's syndrome • Stevens-Johnson syndrome • Uveitis

Table S4 Adverse events of special interest for SARS-CoV-2 vaccines

Based on Brighton Collaboration via CEPI's Safety Platform for Emergency vACcines (SPEAC) Project

Immunological disorders:	• Anaphylaxis • Vasculitides • Vaccine-associated enhanced diseases (VAED)
Respiratory disorders:	• Acute respiratory distress syndrome
Cardiac disorders:	• Acute cardiac injury including: • Microangiopathy • Heart failure and cardiogenic shock • Stress cardiomyopathy • Coronary artery disease • Arrhythmia • Myocarditis, pericarditis
Haematological disorders:	• Thrombocytopenia
Coagulation disorder:	• Deep vein thrombosis • Pulmonary embolus • Cerebrovascular stroke • Limb ischemia • Haemorrhagic disease
Renal disorders:	• Acute kidney injury
Gastrointestinal disorders	• Liver injury
Neurological disorders:	• Generalized convulsion • Guillain-Barré Syndrome • Acute disseminated encephalomyelitis • Meningoencephalitis • Dermatologic disorder: • Chilblain-like lesions • Single organ cutaneous vasculitis • Erythema multiforme
Other:	• Serious local/systemic AR following immunisation

Table S5 Summary of reasons for discontinuing treatment or the study

The results are shown as n (%).

	CVnCoV N=19 783	**Placebo N=19 746**
Completed treatment	19 437 (98·3)	18 498 (93·7)
Discontinued treatment	317 (1·6)	1201 (6·1)
Adverse event	23 (0·1)	18 (<0·1)
Died	2 (<0·1)	4 (<0·1)
Physician decision	21 (0·1)	73 (0·4)
Pregnancy	5 (<0·1)	9 (<0·1)
Protocol deviation	9 (<0·1)	14 (<0·1)
Withdrawal by subject	135 (0·7)	541 (2·7)
SARS-CoV-2 infection	42 (0·2)	63 (0·3)
Other	80 (0·4)	479 (2·4)
Discontinued study	397 (2·0)	3534 (17·9)
Adverse event	5 (<0·1)	4 (<0·1)
Subject received alternative authorised vaccine	161 (0·8)	2558 (13·0)
Physician decision	11 (<0·1)	17 (<0·1)
Study terminated by sponsor	1 (<0·1)	0
Withdrawal by subject	170 (0·9)	795 (4·0)
Lost to follow up	29 (0·1)	33 (0·2)
Other	20 (0·1)	127 (0·6)

Table S6 List of study endpoints, including endpoints not included those that will be analysed at study end

Primary Endpoints	
Primary Efficacy Endpoint	
Occurrence of first episodes of virologically-confirmed {reverse transcription polymerase chain reaction (RT-PCR) positive} cases of COVID-19 of any severity meeting the case definition for the primary efficacy analysis	Included in manuscript
Primary Safety Endpoints	
Occurrence, intensity and relationship of medically-attended AEs collected through 6 months after the second trial vaccination in all subjects	Will be done in final analysis
Occurrence, intensity and relationship of SAEs and AESIs collected through 1 year after the second trial vaccination in all subjects	Included in manuscript*
Occurrence of fatal SAEs through 1 year after the second trial vaccination in all subjects	Included in manuscript*
Occurrence, intensity and duration of each solicited local AE within 7 days after each trial vaccination in Phase 2b subjects	Included in manuscript
Occurrence, intensity, duration of each solicited systemic AE within 7 days after each trial vaccination in Phase 2b subjects	Included in manuscript
Occurrence, intensity and relationship of unsolicited AEs occurring within 28 days after each trial vaccination in Phase 2b subjects	Included in manuscript
Occurrence of AEs leading to vaccine withdrawal or trial discontinuation through 1 year after the second trial vaccination in all subjects	Will be done in final analysis
Secondary Endpoints	
Key Secondary Efficacy Endpoints	
Occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of moderate to severe COVID-19 meeting the case definition for the primary efficacy analysis	Included in manuscript
Occurrence of first episodes of virologically-confirmed (RT-PCR positive) severe cases of COVID-19 meeting the case definition for the primary efficacy analysis	Included in manuscript
Occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity meeting the case definition due to infection with 'wild type' and 'UK' SARS-CoV-2 strains in SARS-CoV-2 naïve subjects	Will not be done as only 7 cases with wild-type infection
Occurrence of seroconversion to the N protein of SARS-CoV-2 $\geq$ 15 days following the second trial vaccination in asymptomatic seronegative subjects	Will be done in final analysis
Other Secondary Efficacy Endpoints	
In subjects $\geq$ 61 years of age, occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity meeting the case definition for the primary efficacy analysis	Included in manuscript
Occurrence of virologically-confirmed (RT-PCR positive) SARS-CoV-2 infection, with or without symptoms	Will be done in final analysis
BoD scores calculated based on first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity meeting the case definition for the primary efficacy analysis	Will be done in final analysis
Occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity with symptom onset at any time after the first trial vaccination	Will be done in final analysis
Secondary Immunogenicity Endpoints (Phase 2b Immunogenicity Subset)	
SARS-CoV-2 RBD of S protein antibody responses On Days 1, 29, 43, 57, 120, 211 and 393: Serum antibodies to SARS-CoV-2 RBD of S protein. Occurrence of seroconversion to SARS-CoV-2 RBD of S protein.	Will be done in final analysis
SARS-CoV-2 viral neutralizing antibody responses On Days 1, 29, 43, 57, 120, 211, and 393: Serum viral neutralizing antibodies to SARS-CoV-2 virus, as measured by a viral neutralizing antibody assay. Occurrence of seroconversion to SARS-CoV-2 virus, as measured by a viral neutralizing antibody assay.	Will be done in final analysis

* Data analysed up to database lock (June 18 2021).

Table S7 SARS-CoV-2 variants sequenced in the efficacy analysis set during the HERALD clinical trial

Pangolin lineage	WHO label	Variant of concern or interest
P.2		
P.1.2		
P.1	Gamma	Variant of concern
C.37	Lambda	Variant of interest
C.36		
B.1.623		
B.1.621	Mu	Variant of interest
B.1.617.2	Delta	Variant of concern
B.1.526		
B.1.177		
B.1.1.7	Alpha	Variant of concern
B.1.1.519		
B.1.1.1		
B.1		
A.2.5		

Table S8 Solicited local and systemic adverse events in the Phase 2b reactogenicity analysis set
Solicited local and systemic adverse events were reported for 7 days following dose 1 and dose 2 using participant diaries. [a]in participants reporting a reaction, reported as median (IQRx) days

	CVnCoV		Placebo	
	Dose 1 N=2003	**Dose 2** N=1964	**Dose 1** N=1978	**Dose 2** N=1908
Local adverse events				
Pain, n (%)	1502 (75·0)	1322 (67·3)	279 (14·1)	220 (11·6)
Median duration[a]		2 (1·0–3·0)		1 (1·0–2·0)
Grade 3, n (%)	15 (0·7)	10 (0·5)	0	1 (<0·1)
Median duration[a]		1 (1·0–1·0)		14 (14–14)
Swelling, n (%)	93 (4·6)	82 (4·2)	13 (0·7)	6 (0·3)
Median duration[a]		1 (1·0–2·0)		1 (1·0–2·0)
Grade 3, n (%)	1 (<0·1)	1 (<0·1)	0	0
Median duration[a]		1 (1–1)		
Redness, n (%)	60 (3·0)	40 (2·06)	20 (1·0)	7 (0·4)
Median duration[a]		1 (1.0–3.0)		14 (1·0–3·0)
Grade 3, n (%)	2 (<0·1)	0	0	0
Median duration[a]		1 (1–1)		
Itching, n (%)	82 (4·1)	75 (3·8)	64 (3·2)	41 (2·1)
Median duration[a]		1 (1·0–2·0)		1 (1·0–2·0)
Grade 3, n (%)	0	0	0	0
Median duration[a]				
Systemic adverse events				
Fatigue, n (%)	1339 (66·8)	1283 (65·3)	657 (33·2)	474 (24·8)
Median duration[a]		2 (1·0–2·0)		1 (1·0–2·0)
Grade 3, n (%)	154 (7·7)	176 (9·0)	26 (1·3)	14 (0·7)
Median duration[a]		1 (1·0–1·0)		1 (1·0–2·0)
Headache, n (%)	1269 (63·4)	1268 (64·6)	623 (31·5)	413 (21·6)
Median duration[a]		1 (1·0–2·0)		1 (1·0–2·0)
Grade 3, n (%)	126 (6·3)	143 (7·3)	11 (0·6)	4 (0·2)
Median duration[a]		1 (1·0–1·0)		1 (1·0–2·0)
Myalgia, n (%)	1055 (52·7)	976 (49·7)	286 (14·5)	165 (8·6)
Median duration[a]		1 (1·0–2·0)		1 (1·0–1·0)
Grade 3, n (%)	57 (2·8)	99 (5·0)	6 (0·3)	4 (0·2)
Median duration[a]		1 (1·0–1·0)		1 (1·0–1·0)
Chills, n (%)	708 (35·4)	732 (37·3)	111 (5·6)	74 (3·9)
Median duration[a]		1 (1·0–1·0)		1 (1·0–1·0)
Grade 3, n (%)	122 (6·1)	135 (6·9)	3 (0·2)	1 (<0·1)
Median duration[a]		1 (1·0–1·0)		1 (1·0–1·0)
Arthralgia, n (%)	369 (18·4)	394 (20·1)	113 (5·7)	57 (3·0)
Median duration[a]		1 (1·0–2·0)		1 (1·0–2·0)
Grade 3, n (%)	22 (1·1)	40 (2·0)	4 (0·2)	3 (0·2)
Median duration[a]		1 (1·0–1·0)		1 (1·0–1·0)
Fever, n (%)	368 (18·4)	462 (23·5)	8 (0·4)	5 (0·3)
Median duration[a]		1 (1·0–1·0)		1 (1·0–1·0)
Grade 3, n (%)	30 (1·5)	67 (3·4)	0	0
Median duration[a]		1 (1·0–1·0)		
Nausea/vomiting, n (%)	260 (13·0)	262 (13·3)	102 (5·2)	69 (3·6)
Median duration[a]		1 (1·0–2·0)		1 (1·0–1·0)
Grade 3, n (%)	9 (0·4)	6 (0·3)	1 (<0·1)	0
Median duration[a]		1 (1·0–1·0)		
Diarrhoea, n (%)	246 (12·3)	201 (10·2)	142 (7·2)	108 (5·7)
Median duration[a]		1 (1·0–2·0)		1 (1·0–1·0)
Grade 3, n (%)	7 (0·3)	5 (0·3)	1 (<0·1)	3 (0·2)
Median duration[a]		1 (1·0–1·0)		1 (1·0–1·0)

Figure S1 Trial profile for the phase 2b part of the trial

[a]In theCVnCoV group, 13 participants were censored from the safety analysis set 2 and two were excluded from the reactogenicity analysis because diary data were missing. In the placebo group, two participants were censored from the safety analysis set 2 and eight were excluded from the reactogenicity analysis because diary data were missing.