Annexes to the recommendations for use of the Valneva VLA2001 vaccine against COVID-19

Grading of evidence

Evidence to recommendations tables

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Background

These are the annexes to the Interim recommendations for use of the Valneva VLA2001 vaccine against COVID-19.

Annexes 1–6 contain tables that summarize the grading of recommendations, assessment, development and evaluations (GRADE). Annexes 7–9 contain the SAGE evidence-to-recommendation framework tables (ETR tables). The ETR tables are based on the DECIDE Work Package 5: Strategies for communicating evidence to inform decisions about health system and public health interventions. Evidence to a recommendation (for use by a guideline panel) (www.decide-collaboration.eu/, accessed 9 December 2021).

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Annex 1. GRADE table: Efficacy of VLA2001 COVID-19 vaccine in adults

Population:	Adults (18–50 years)
Intervention:	Two doses of VLA2001 vaccine
Comparison:	Placebo/active control
Outcome:	COVID-19 (PCR-confirmed)

What is the efficacy of two doses of VLA2001 vaccine compared with placebo/active control in preventing PCR-confirmed COVID-19 in adults (18–50 years)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT *(1)*	4
	Factors decreasing confidence	Limitation in study design[a]	Not serious	0
		Inconsistency	Not serious	0
		Indirectness	Serious[b]	-2
		Imprecision	Not serious	0
		Publication bias	Not serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**2**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a limited level of confidence that the true effect lies close to the estimate of the effect on the health outcome (level 2).**
	Conclusion			Vaccine efficacy in adults (18–50 years) is inferred by demonstrating a non-inferior immune response between VLA2001 vaccine and ChAdOx1-S vaccine for which efficacy against PCR-confirmed COVID-19 has been estimated. The confidence in the quality of evidence is limited due to indirectness of the data.

[a] For the risk of bias assessments using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), please see www.covid-nma.com/vaccines.

[b] No efficacy estimates were obtained. Protection of VLA2001 vaccine is inferred by immunobridging to ChAdOx1-S vaccine. Participants ⩾30 years were randomized to either vaccine, participants aged <30 years received two doses of VLA2001 open label. This was considered as constituting a limitation that leads to downgrading of the evidence.

Annex 2. GRADE table: Safety of VLA2001 vaccine in adults

Population:	Adults (18–50 years)			
Intervention:	One or two doses of VLA2001 vaccine			
Comparison:	Placebo/active control			
Outcome:	Serious adverse events following immunization			
What is the risk of serious adverse events following VLA2001 vaccination compared with placebo/active control in adults (18–50 years)?				
			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		2/ RCT *(1, 2)*	4
	Factors decreasing confidence	Limitation in study design[a]	Serious[b]	-1
		Inconsistency	Not serious	0
		Indirectness	Not serious	0
		Imprecision	Not serious	0
		Publication bias	Not serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**3**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a moderate level of confidence that the true effect lies close to the estimate of the effect on the health outcome (level 3).**
	Conclusion			We are moderately confident that there is a very low risk of serious adverse events following one or two doses of VLA2001 vaccine in adults (18–50 years) .

Annex 3. GRADE table: Efficacy of VLA2001 COVID-19 vaccine in older adults

[a] For the risk of bias assessments using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), please see www.covid-nma.com/vaccines.

[b] Downgraded for the following limitations. The trials were not adequately powered to detect rare adverse events (i.e. fewer than about 1 in 2000).

Population:	Older adults (≥50 years)
Intervention:	Two doses of VLA2001 vaccine
Comparison:	Placebo/active control
Outcome:	COVID-19 (PCR-confirmed)

What is the efficacy of two doses of VLA2001 vaccine compared with placebo/active control in preventing PCR-confirmed COVID-19 in older adults (≥50 years)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT *(1)*	4
	Factors decreasing confidence	Limitation in study design[a]	Not serious	0
		Inconsistency	Not serious	0
		Indirectness	Serious[b]	-2
		Imprecision	Serious[c]	-1
		Publication bias	Not serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**1**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports very low confidence that the true effect lies close to the estimate of the effect on the health outcome (level 1).**
	Conclusion			Vaccine efficacy in older adults (≥55 years) is inferred by demonstrating a non-inferior immune response between VLA2001 vaccine and ChAdOx1-S vaccine for which efficacy against PCR-confirmed COVID-19 has been estimated. The confidence in the quality of evidence is very low due to indirectness of the data and limited representation of older adults.

[a] For the risk of bias assessments using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), please see www.covid-nma.com/vaccines.

[b] No efficacy estimates were obtained. Protection of VLA2001 vaccine is inferred by immunobridging to ChAdOx1-S vaccine. This was considered as constituting limitations that lead to downgrading of the evidence.

[c] In the phase 3 trial, less than 1% of the population studied was older than 50 years leading to wide confidence intervals. This was considered as constituting a limitation that leads to downgrading of the evidence

Annex 4. GRADE table: Safety of VLA2001 COVID-19 vaccine in older adults

Population:	Older adults (≥50 years)
Intervention:	One or two doses of VLA2001 vaccine
Comparison:	Placebo/active control
Outcome:	Serious adverse events following immunization

What is the risk of serious adverse events following VLA2001 vaccination compared with placebo/active control in older adults (≥50 years)?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT *(1)*	4
	Factors decreasing confidence	Limitation in study design[a]	Serious[b]	-1
		Inconsistency	Not serious	0
		Indirectness	Serious[c]	-2
		Imprecision	Not serious	0
		Publication bias	Not serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**1**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a very low level of confidence that the true effect lies close to the estimate of the effect on the health outcome (level 1).**
	Conclusion			We have very low confidence that the risk of serious adverse events following one or two doses of VLA2001 vaccine in older adults (≥50 years) is low.

[a] For the risk of bias assessments using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), please see www.covid-nma.com/vaccines.

[b] Downgraded for the following limitations. The trial was not adequately powered to detect rare adverse events (i.e. fewer than about 1 in 2000).

[c] In the phase 3 clinical trial, less than 1% of the population studied was older than 50 years. This was considered as constituting a limitation that leads to downgrading of the evidence.

Annex 5. GRADE table: Efficacy of VLA2001 COVID-19 vaccine in individuals with underlying conditions

Population:	Individuals with comorbidities or health states that increase risk for severe COVID-19
Intervention:	Two doses of VLA2001 vaccine
Comparison:	Placebo/active control
Outcome:	COVID-19 (PCR-confirmed)

What is the efficacy of two doses of VLA2001 vaccine compared with placebo/active control in preventing PCR-confirmed COVID-19 in individuals with comorbidities or health states that increase risk for severe COVID-19?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT *(1)*	4
	Factors decreasing confidence	Limitation in study design[a]	Not serious	0
		Inconsistency	Not serious	0
		Indirectness	Serious[b]	-2
		Imprecision	Serious[c]	-1
		Publication bias	Not serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**1**
Summary of Findings	**Statement on quality of evidence**			**Evidence supports a very low level of confidence that the true effect lies close to the estimate of the effect on the health outcome (level 1).**
	Conclusion			Vaccine efficacy in individuals with comorbidities or health states that increase risk for severe COVID-19 is inferred by demonstrating a non-inferior immune response between VLA2001 vaccine and ChAdOx1-S vaccine for which efficacy against PCR-confirmed COVID-19 has been estimated. No data were obtained from the clinical trial on vaccination of pregnant or breastfeeding

[a] For the risk of bias assessments using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2), please see www.covid-nma.com/vaccines.

[b] No efficacy estimates were obtained. Protection of VLA2001 vaccine is inferred by immunobridging to ChAdOx1-S vaccine. This was considered as constituting a limitation that leads to downgrading of the evidence.

[c] The phase 3 trial included mainly healthy adults. Few individuals with comorbidities were included, leading to wide confidence intervals. Underlying comorbidities included BMI ≥ 30 kg/m2, cardiovascular disorder, respiratory disease and diabetes. Trial excluded pregnant and breastfeeding women, and persons who were immunocompromised. This was considered as constituting a limitation that leads to downgrading of the evidence.

		women, or persons who were immunocompromised. The confidence in the quality of evidence is very low due to indirectness of the data and limited representation of older adults.

Annex 6. GRADE table: Safety of VLA2001 COVID-19 vaccine in individuals with underlying conditions

Population:	Individuals with comorbidities or health states that increase risk for severe COVID-19
Intervention:	One or two doses of VLA2001 vaccine
Comparison:	Placebo/active control
Outcome:	Serious adverse events following immunization

What is the risk of serious adverse events following VLA2001 vaccination compared with placebo/active control in individuals with underlying conditions?

			Rating	Adjustment to rating
Quality Assessment	No. of studies/starting rating		1/ RCT *(1)*	4
	Factors decreasing confidence	Limitation in study design[a]	Serious[b]	-1
		Inconsistency	Not serious	0
		Indirectness	Serious[c]	-2
		Imprecision	Not serious	0
		Publication bias	Not serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			**1**
mary of Findings	**Statement on quality of evidence**			**Evidence supports a very low level of confidence that the true effect lies close to the estimate of the effect on the health outcome (level 1).**
	Conclusion			We have very low confidence that the risk of serious adverse events following one or two doses of VLA2001 vaccine in individuals with comorbidities or health states that increase risk