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SCIENCE MEDICINES HEALTH

COVID-19 Update on development of therapeutics and vaccines for paediatric use

Enpr-EMA
European network of paediatric research at the European Medicines Agency

Enpr-EMA meeting, 28 September 2021

Laura Fregonese
Paediatric Medicines and COVID19 Task Force

Agreed COVID Vaccine PIPs (I)

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Vaccine	Study 1	Study 2	Study 3
Comirnaty (Biontech/Pfizer)	Double blind placebo-controlled efficacy, safety and immunogenicity study in adolescents from 12 years to less than 18 years of age (and adults) (part 2) (C4591001) [redacted] Data used for current MA PE: NI immunogenicity (NA) vs young adults	Double blind, controlled safety and immunogenicity study of BNT162b2 in children from 6 months to less than 12 years of age for prevention of COVID-19 (C4591007) Data in 5-11 years soon to be submitted for MAA [redacted] PE: NI immunogenicity (NA) vs 16-25 yrs	Double blind, controlled, dose-finding, safety and immunogenicity study of BNT162b2 in children from birth to less than 6 months of age for prevention of COVID-19 RDM 1:1 concomitant or separate from routine vaccine schedules PE: NI immunogenicity (NA) vs 16-25 yrs
Vaxzevria Astra Zeneca	Randomised, observer-blind, controlled study to evaluate safety and immunogenicity of Vaxzevria in children and adolescents from birth to less than 12 years of age. Dose finding PE: NI immunogenicity (NA) vs young adults	Randomised, observer-blind, controlled study to evaluate the safety and immunogenicity of Vaxzevria for prevention of COVID-19 in children from birth to less than 12 years of age. Confirmatory phase 28-days or 84-days vaccine schedule PE: NI immunogenicity (NA) vs young adults	**NEW** Randomised controlled study to evaluate safety and immunogenicity of Vaxzevria for prevention of COVID-19 in adolescents from 12 to less than 18 years of age 28-days or 84-days vaccine schedule PE: NI immunogenicity (NA) vs 18-25 yrs
Spikevax Moderna	Randomized, observer-blind, placebo-controlled, study to evaluate safety, reactogenicity, and immunogenicity in adolescents from 12 to less than 18 years of age [redacted] PE: NI immunogenicity (NA) vs young adults	Randomized, observer-blind, placebo-controlled, study to evaluate dose finding (part 1), and safety, reactogenicity, and immunogenicity (part 2) of mRNA-1273 in children from birth to less than 12 years of age for prevention of COVID-19. part 1: dose finding; part 2: dose expansion [redacted] PE: NI immunogenicity (NA) vs young adults	

Agreed COVID Vaccine PIPs (II)

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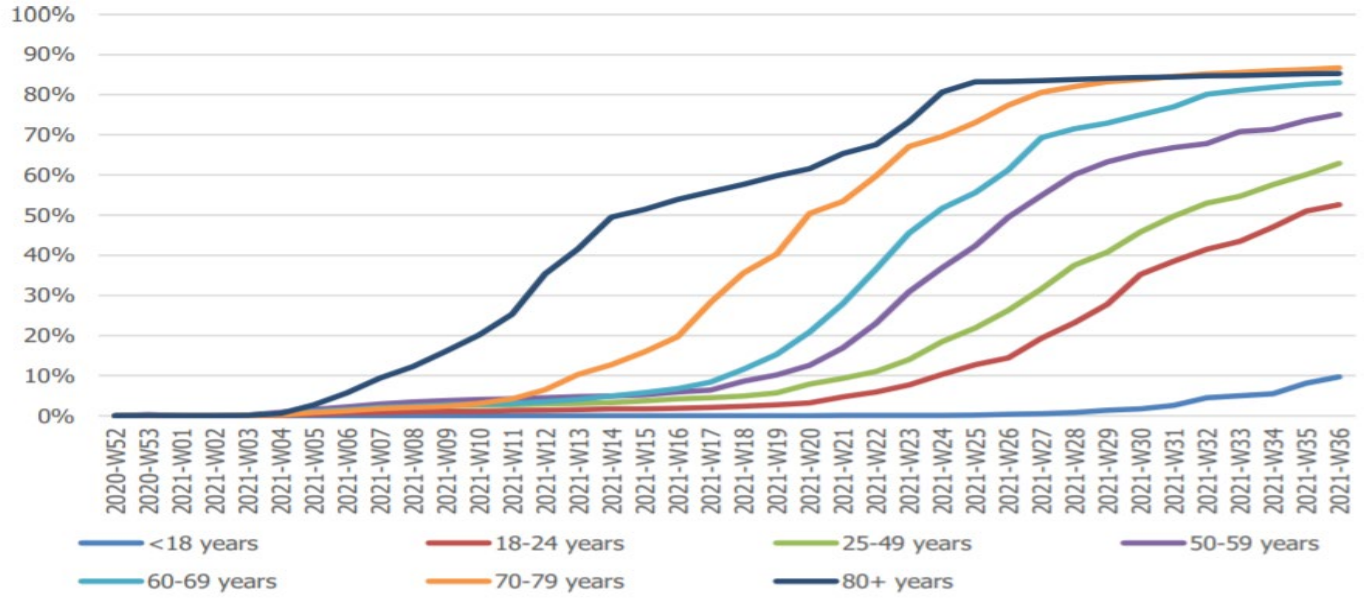
Vaccine	Study 1	Study 2	Study 3
Ad26.COV2-S COVID-19 vaccine Janssen	Randomised, double-blind, controlled study to evaluate safety, reactogenicity and immunogenicity of different dose levels of Ad26.COV2-S (1 or more doses) in healthy adolescents from 12 to less than 18 years of age (and adults) for the prevention of COVID-19 Completion: March 2023	Randomised, double-blind, controlled study to evaluate the safety, reactogenicity and immunogenicity of Ad26.COV2-S (recombinant) in healthy children from birth to less than 18 years of age (and adults) for the prevention of COVID-19 (VAC31518COV3006) Completion: March 2024	
NUVAXOVID Novavax, Inc.	Randomised, observer-blinded, active-controlled study to evaluate safety and immunogenicity of SARS-CoV-2 rS) / matrix-M1 adjuvant in adolescents from 12 to less than 18 years of age (and adults) ((2019nCoV-502) Completion: March 2022	Randomised, observer-blinded, controlled study to evaluate efficacy, safety and immunogenicity of SARS-CoV-2 rS) / matrix-M1 adjuvant in paediatric participants from 6 to less than 18 years of age (and adults). Paediatric participants enrolled in Part 2 (Paediatric expansion) (safety and immunogenicity only) (2019nCoV-301)	Randomised, observer-blinded, controlled study to evaluate the safety and immunogenicity of SARS-CoV-2 rS) / matrix-M1 adjuvant in paediatric participants from birth to less than 6 years of age (2019nCoV-503) Completion: March 2024
SARS-CoV2 prefusion spike delta adjuvanted with AS03 Sanofi Pasteur	Randomised, modified double-blind, controlled immunogenicity and safety study of SARS-CoV2 prefusion spike delta TM (CoV-2 preS dTM) adjuvanted with AS03 versus active vaccine comparator or placebo in children from birth to less than 18 years of age. (VAT00003) Completion: December 2024		
Zorecimeran Curevac AG	Randomised, controlled, dose-confirmation trial to evaluate safety and immunogenicity of 2 dose levels of zorecimeran in adolescents from 12 years to less than 18 years of age for the prevention of COVID-19	Randomised controlled trial to evaluate safety and immunogenicity of zorecimeran in adolescents from 12 years to less than 18 years of age for the prevention of COVID-19 (confirmatory study)	Randomised, observer-blind, controlled trial to evaluate the safety, reactogenicity and immunogenicity of zorecimeran (CVnCoV) in children from birth to less than 12 years of age for the prevention of COVID-19

Updates on Principles of COVID vaccines' PIPs

- Age- descending approach (safety and reactogenicity)
- Development from birth to be discussed after all other age cohorts
- Careful approach to dosing- also retrospective based on emerging safety profile
- Immuno-bridging with adult data (non-inferiority; neutralizing antibodies)
- Children with chronic conditions can be enrolled plus ad hoc studies for immunocompromised children
- Second year of follow-up requested, but not part of completion of the studies
- Cross-over of placebo to active possible after 6 months
- End date on EMA website refers to end of the whole PIP

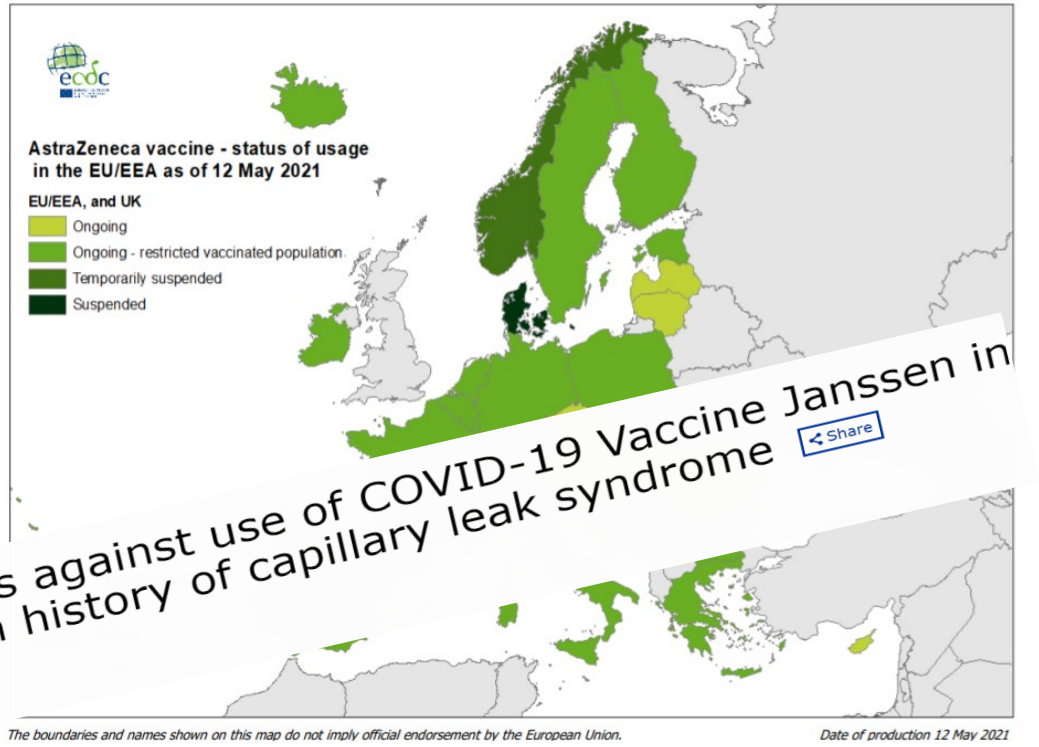
Uptake of authorized COVID vaccines for paediatrics in EU

Figure 5. Median cumulative of full vaccination uptake by age group, as of week 36, 2021 (27 reporting countries, see below)



Paediatric trials with Adv COVID vaccines?

- No AZ trials started in the EU in adolescents/paediatric populations- Oxford trial (started Feb 21 in UK) was suspended
- Janssen phase 2 adolescents/adults was ongoing in some EU countries last spring- approx. 30 adolescents with no AEs
- Paediatric studies to be re-discussed with progress in understandi
mechanisms and risk factor



EMA advises against use of COVID-19 Vaccine Janssen in people with history of capillary leak syndrome

Share

News 09/07/2021

Recommendations for mRNA vaccines in paediatrics *vis a vis* myocarditis

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- CDC continues to recommend COVID-19 vaccination for everyone 12 years of age and older given the greater risk of other serious complications related to COVID-19, such as hospitalization, multisystem inflammatory syndrome in children (MIS-C), or death.
- Consider myocarditis and pericarditis in adolescents or young adults with acute chest pain, shortness of breath, or palpitations. In this younger population, coronary events are less likely to be a source of these symptoms.
- Ask about prior COVID-19 vaccination if you identify these symptoms, as well as relevant other medical, travel, and social history.
- For initial evaluation, consider an ECG, troponin level, and inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate. In the setting of normal ECG, troponin, and inflammatory markers, myocarditis or pericarditis are unlikely.

8 September 2021

COVID-19 vaccine safety update

Myocarditis and pericarditis

No further update to the Comirnaty product information at present

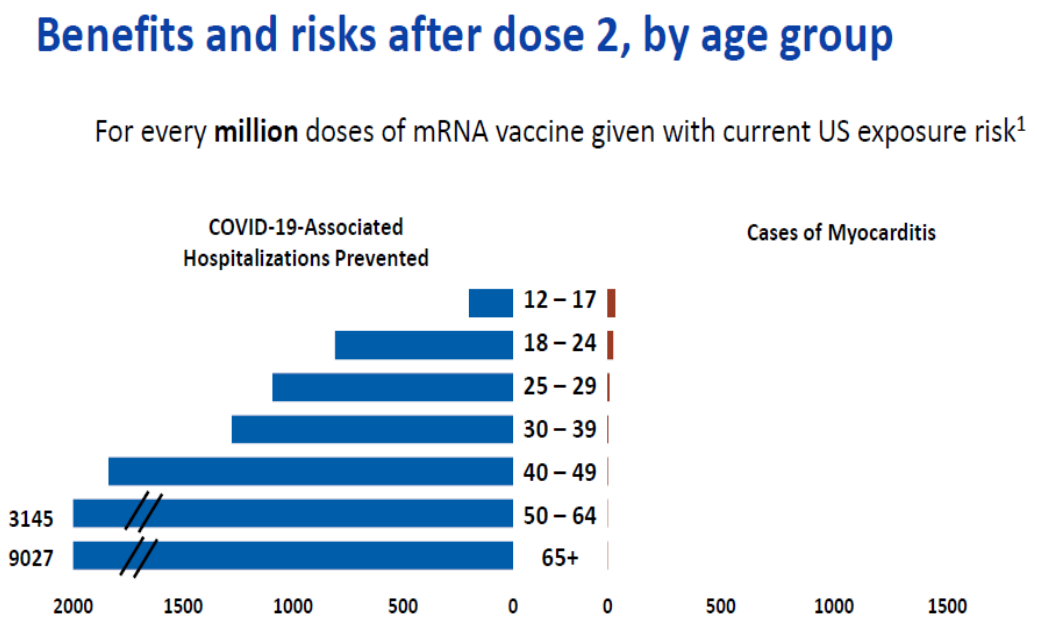
Myocarditis and pericarditis were added to the product information of Comirnaty in the side effects and warning sections, following the assessment by PRAC in July 2021[3].

Myocarditis and pericarditis are inflammatory conditions of the heart.

PRAC has kept these conditions under close monitoring and in September 2021 concluded that so far there is no new information on which base to change the current recommendation regarding the second vaccination in people who experienced myocarditis or pericarditis after the first dose or any other aspects of these side effects.

Myocarditis and paediatric benefit-risk of mRNA COVID vaccines

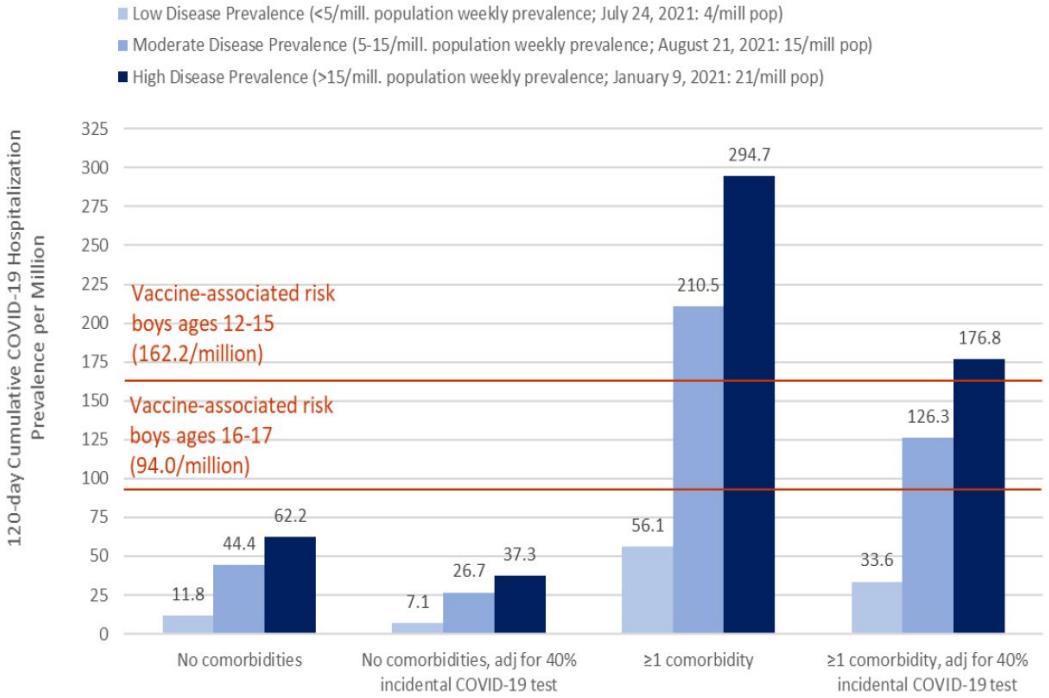
- Occurs after mRNA COVID-19 vaccination (Pfizer-BioNTech or Moderna), especially in male adolescents and young adults
- More often after the second dose
- Usually within several days after vaccination (4-5 days)
- US rate 12.6 cases per million 2nd doses
- Most cases mild in severity
- Sequelae?



Dimension needs to be clarified, but beware non-peer reviewed articles

SARS-CoV-2 mRNA Vaccination-Associated Myocarditis in Children Ages 12-17:A Stratified National Database Analysis

Tracy Beth Høeg, Allison Krug, Josh Stevenson, John Mandrola



Limitations

Description of the methods is largely inadequate

Using VAERs data to produce event rates is challenging

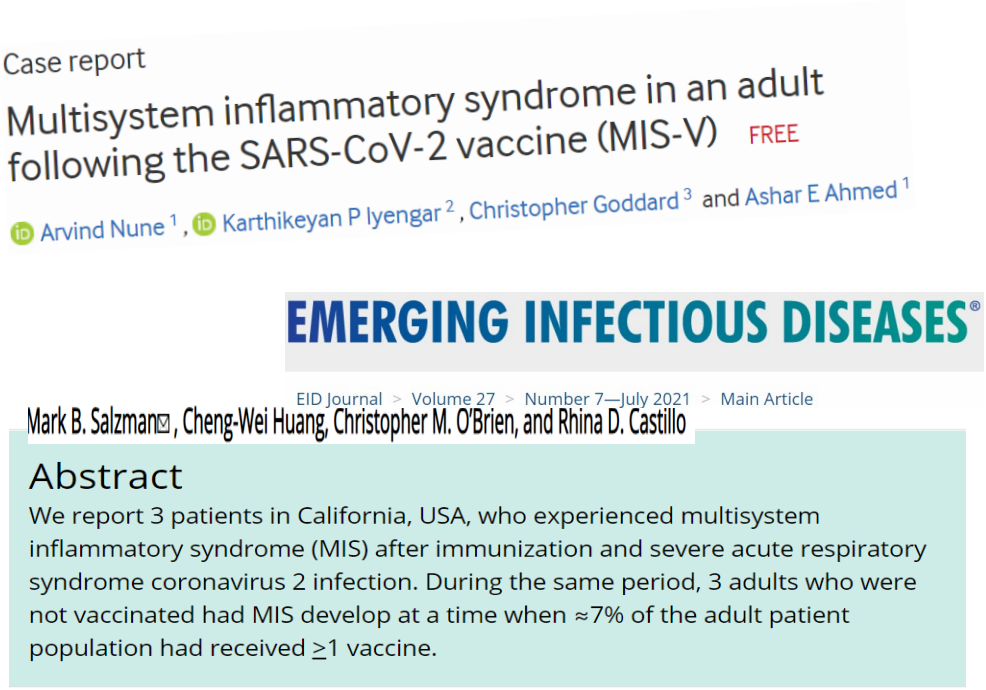
Event rates are much higher than those reported by CDC using the same VAERS data

Appropriateness of using VAERS data to fit CDC defined "probable myocarditis" endpoint is questionable

"risk-benefit analysis" is extremely crude

No sensitivity analysis to assess the potential impact of the many assumption made

MIS-C after vaccination?



Case report

Multisystem inflammatory syndrome in an adult following the SARS-CoV-2 vaccine (MIS-V) FREE

Arvind Nune [1], Karthikeyan P Iyengar [2], Christopher Goddard [3] and Ashar E Ahmed [1]

EMERGING INFECTIOUS DISEASES®

EID Journal > Volume 27 > Number 7—July 2021 > Main Article

Mark B. Salzman, Cheng-Wei Huang, Christopher M. O'Brien, and Rhina D. Castillo

Abstract

We report 3 patients in California, USA, who experienced multisystem inflammatory syndrome (MIS) after immunization and severe acute respiratory syndrome coronavirus 2 infection. During the same period, 3 adults who were not vaccinated had MIS develop at a time when ≈7% of the adult patient population had received ≥1 vaccine.

- MIS-C Cases to 19th August 2021 in the EEA from EudraVigilance database: Comirnaty: 5; Spikevax: 1; Vaxzevria: no case; COVID-19 Vaccine Janssen: 1
- Signals so far rare
- MIS-C part of the monitored AEs post-marketing (e.g. ACCESS; SPEAC)
- Signal investigation ongoing at EMA

Vaccination of pregnant women (credit: Kelly Plueschke, EMA)

- To date, data on COVID-19 vaccines and treatments in pregnancy are **very scarce**
- Current data show :
  - That pregnant women with COVID-19 are at **higher risk** of severe disease and adverse (P) outcomes
  - **No obvious safety signals** with respect to pregnancy/neonatal outcomes associated with vaccination
- Importance of **safety monitoring** via routine and additional PhV measures + Clinical studies
- **International collaboration (ICMRA and other stakeholders) is key to share information, data, experience and leverage this knowledge to develop a global strategy to protect public health**
- EMA pregnancy strategy

Agreed COVID Therapeutics PIPs (I)

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Antiviral monoclonal antibodies	Study 1	Study 2	Study 3	Study 4
Casirivimab and Indevimab (RONAPREVE) **Regeneron** **TREATMENT INDICATION** **PIP supports IV and SC use**	(PK), safety and tolerability study of single-dose casirivimab and imdevimab for the treatment of COVID-19 in paediatric patients from birth to less than 18 years of age who are at risk of severe disease.	Open-label, single-dose study to evaluate safety, tolerability and PK of casirivimab and imdevimab for the treatment of paediatric patients from 29 weeks gestational age (at birth) to less than 18 years of age with COVID-19 who require hospitalisation.	PopPK model for dosing prediction and confirmation for the intravenous (IV) and subcutaneous (SC) routes of administration in paediatric patients from 29 weeks of gestational age (at birth) (GA) to less than 18 years of age.	PK bridging and extrapolation of safety and efficacy to support the use of a single-dose of casirivimab and imdevimab administered intravenously (IV) for the treatment of COVID-19 from adults to children from 29 weeks gestational age (at birth) to less than 18 years of age.
Casirivimab and Indevimab (RONAPREVE) **Regeneron** **PREVENTION INDICATION** **PIP supports IV and SC use**	Randomized, double-blinded, placebo-controlled study of casirivimab and imdevimab to evaluate efficacy, safety and tolerability in asymptomatic adolescents (and adults) who are household contacts of a person infected with SARS-CoV-2 and are SARSCoV-2 RT-qPCR negative at baseline (Cohort A) or SARS-CoV-2 RT-qPCR positive at baseline (Cohort B)	Open-label, single-dose study to assess the pharmacokinetics, safety, and tolerability of a single-dose of subcutaneous casirivimab and imdevimab in paediatric subjects from birth to less than 12 years of age.	same as above	Same as above
Sotrovimab **GSK** **PIP supports IV use**	Open-label, non-comparator, multicentre study to describe pharmacokinetics (PK), pharmacodynamics (viral load) and safety following a single intravenous dose of sotrovimab in paediatric participants from 32 weeks gestational age (GA) with mild to moderate COVID-19 at high risk of progression.	Population PK (PopPK) model for dosing prediction and confirmation in paediatric patients from 32 weeks of gestational age (GA) (at birth) to less than 18 years of age.	PK bridging and extrapolation of safety and virology data to support the use of sotrovimab for the treatment of mild, moderate COVID-19 disease in children from 32 weeks GA (at birth) to less than 18 years of age.	
Bamlanivimab and etesevimab **Ely Lilly** **PIP supports IV use**	Randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of bamlanivimab in combination with etesevimab for the treatment of adolescents (and adults) with mild or moderate COVID-19, who are at increased risk of adverse outcomes and severe COVID-19.	Multicentre, single arm, open-label study to evaluate pharmacokinetics (PK) and safety of bamlanivimab and etesevimab in children from birth to less than 18 years of age with mild or moderate COVID-19 who are at increased risk of adverse outcomes and severe COVID-19.	PopPK model for bamlanivimab and etesevimab dosing predictions and confirmation in paediatric patients from 32 weeks of gestational and 1.5 kg of weight to less than 18 years of age.	Extrapolation analyses to support efficacy and safety assumptions for bamlamivimab in combination with etesevimab in the paediatric population from 32 weeks gestational age to less than 18 years of age with mild to moderate COVID-19 at risk of developing severe disease from adult patients with mild to moderate COVID-19 at risk of developing

Agreed COVID Therapeutics PIPs (II)

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Antiviral monoclonal antibodies	Study 1	Study 2	Study 3	Study 4
Regdanvimab **Celltrion** **PIP supports IV use**	Single-arm, open-label study to evaluate the safety, tolerability, pharmacokinetics, and efficacy of regdanvimab in combination with standard of care (SoC) in paediatric patients from birth to less than 18 years of age with mild or moderate COVID-19 who are at increased risk of adverse outcomes and severe COVID-19	Modelling and simulation study to characterise the pharmacokinetics (PK) of regdanvimab, to perform dose selection as well as exposure predictions in support of extrapolation of efficacy from adults to paediatric patients		
Cilgavimab and tixagevimab **Astra Zeneca** **TREATMENT AND PREVENTION INDICATION** **PIP supports IM use**	Open label, uncontrolled, single dose study to evaluate PK, PD and safety of tixagevimab and cilgavimab for the treatment of paediatric patients with mild to moderate COVID-19 at high risk for developing severe disease and for pre and post- exposure prophylaxis in paediatric subjects from 29 weeks gestational age (GA) to less than 18 years of age at high risk of developing severe COVID-19.	Two-compartment population PK (PopPK) model for tixagevimab and cilgavimab dosing prediction and confirmation in paediatric patients from 29 weeks of gestational age (GA) to less than 18 years of age.	PK bridging and extrapolation of clinical efficacy and safety of tixagevimab and cilgavimab for pre- and post-exposure prophylaxis of COVID-19 in paediatric populations from 29 weeks gestational age to less than 18 years of age at risk of developing severe disease.	PK bridging and extrapolation of clinical efficacy and safety of tixagevimab and cilgavimab for treatment of mild-moderate COVID-19 in paediatric patients from 29 weeks gestational age to less than 18 years of age at risk of developing severe disease.
Chemical antivirals	**Study 1**	**Study 2**	**Study 3**	**Study 4**
Veklury (Remdesivir) **Gilead**	Open-label, single-arm study to evaluate the pharmacokinetics, safety, tolerability, and efficacy of remdesivir (RDV) in hospitalized children, from 32 weeks gestational age to less than 18 years of age, with confirmed COVID-19	Population PK modelling and simulation study to determine a paediatric dose/posology in paediatric subjects from 32 weeks gestational age to less than 18 years of age that should achieve the systemic exposures equivalent to that observed in adults	Extrapolation study of efficacy and safety of remdesivir from adult subjects to paediatric patients from 32 weeks gestational age (GA) to less than 18 years of age with confirmed COVID-19	
Molnupiravir Merck Sharp & Dohme	Multicentre, open-label study to evaluate the pharmacokinetics, safety and efficacy of molnupiravir (MK-4482) in children from birth to less than 18 years of age (including premature infants born at least at 32 weeks gestational age) with mild or moderate coronavirus disease 2019.	Population PK modelling and PK/PD exposure-response study to select the molnupiravir (MK-4482) doses across weight bands in children from birth to less than 18 years with coronavirus disease 2019.	Extrapolation study of efficacy and safety of molnupiravir (MK-4482) from adults to children from birth to less than 18 years of age with mild or moderate coronavirus disease 2019.	

Agreed COVID Therapeutics PIPs (III)

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Immunomodulators	Study 1	Study 2	Study 3
Tocilizumab **Roche**	Study 1 Open-label, single arm study to assess the pharmacokinetics (PK), pharmacodynamics (PD), safety and exploratory efficacy of tocilizumab for the treatment of paediatric patients from birth to less than 18 years of age hospitalised with COVID-19	Extrapolation study of pharmacokinetic (PK)/pharmacodynamic (PD) of tocilizumab from adults to paediatric patients with COVID-19 pneumonia based on the analysis of data collected in adult and paediatric patients	Review of available data from published literature or other sources on the use of tocilizumab in paediatric patients from birth to less than 18 years of age with COVID-19 pneumonia.
Baricitinib **Ely Lilly** **(waiver below 1 year of age)**	Open-label, single-arm study to evaluate the pharmacokinetics and safety of baricitinib and to provide PK/PD data to support the extrapolation of efficacy from adults to paediatric patients from 1 year to less than 18 years of age with confirmed COVID-19	Modelling and simulation study to determine and confirm a paediatric dose for baricitinib in paediatric patients from 1 year to less than 18 years of age with confirmed COVID-19 that should achieve an exposure equivalent to that observed in adults	Extrapolation study to support efficacy assumptions for baricitinib in the paediatric population from 1 year to less than 18 years of age with COVID-19 from adult patients with confirmed COVID-19

Principles of COVID treatment PIPs

- Partial extrapolation from adult data accepted but need of PK and safety data collection in children for each administration route and indication (prevention/treatment)
- In principle single arms PK/safety trials (small placebo-controlled arm possible)
- Extrapolation based on similarity of disease/target more difficult for immunomodulators than for antivirals
- PK matching; exposure-response matching at the target (e.g. neutralization from antiviral mAbs); some level of exposure- response data (clinical; viral load)
- Extensive discussions on paediatric populations for pre/post-exposure prophylaxis (children 'at risk')
- Development from birth (including pre-term)

Art 5.3 recommendations for antiviral mAbs include adolescents

REGN-COV2 antibody combination (casirivimab / imdevimab) - COVID19 - Article-5(3) procedure: Conditions of use, conditions for distribution and patients targeted and conditions for safety monitoring (PDF/462.17 KB)

For the treatment of confirmed COVID-19 in patients aged 12 years and older that do not require supplemental oxygen for COVID-19 and who are at high risk of progressing to severe COVID-19.

Risk factors may include but are not limited to:

- Advanced age
- Obesity
- Cardiovascular disease, including hypertension
- Chronic lung disease, including asthma
- Type 1 or type 2 diabetes mellitus
- Chronic kidney disease, including those on dialysis
- Chronic liver disease
- Immunosuppressed, based on prescriber's assessment. Examples include: cancer treatment, bone marrow or organ transplantation, immune deficiencies, HIV (if poorly controlled or evidence of AIDS), sickle cell anaemia, thalassaemia, and prolonged use of immune-weakening medications.

Bamlanivimab alone

Bamlanivimab is indicated for the treatment of confirmed COVID-19 in patients aged 12 years and older that do not require supplemental oxygen for COVID-19 and who are at high risk of progressing to severe COVID-19.

Bamlanivimab administered together with etesevimab

Bamlanivimab and etesevimab administered together are indicated for the treatment of confirmed COVID-19 in patients aged 12 years and older that do not require supplemental oxygen for COVID-19 and who are at high risk of progressing to severe COVID-19

Risk factors may include but are not limited to:

- Advanced age
- Obesity
- Cardiovascular disease, including hypertension
- Chronic lung disease, including asthma
- Type 1 or type 2 diabetes mellitus
- Chronic kidney disease, including those on dialysis
- Chronic liver disease
- Immunosuppressed, based on prescriber's assessment. Examples include: cancer treatment, bone marrow or organ transplantation, immune deficiencies, HIV (if poorly controlled or evidence of AIDS), sickle cell anemia, thalassemia, and prolonged use of immune-weakening medications.

Tocilizumab

Systematic review and meta-analysis of anakinra, sarilumab, siltuximab and tocilizumab for COVID-19 FREE

Fasihul A Khan [1], Iain Stewart [1], Laura Fabbri [1], Samuel Moss [1], Karen Robinson [2], Alan Robert Smyth [3], Gisli Jenkins [1]

Tocilizumab and COVID-19: a meta-analysis of 2120 patients with severe disease and implications for clinical trial methodologies

Azza Sarfraz [1], Zouina Sarfraz [2], Muzna Sarfraz [3], Hinna Aftab [4], Zainab Pervaiz [4]

COMMENT | VOLUME 397, ISSUE 10285, P1599-1601, MAY 01, 2021

Tocilizumab in COVID-19: some clarity amid controversy

Shruti Gupta • David E Leaf

Association Between Administration of IL-6 Antagonists and Mortality Among Patients Hospitalized for COVID-19

A Meta-analysis

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group

Article Information

JAMA. 2021;326(6):49

Findings This prospective meta-analysis of 27 randomized trials included 10 930 patients, of whom 2565 died by 28 days. The 28-day all-cause mortality was lower among patients who received IL-6 antagonists compared with those who received usual care or placebo (summary odds ratio, 0.86). The summary odds ratios for the association of IL-6 antagonist treatment with 28-day all-cause mortality were 0.78 with concomitant administration of corticosteroids vs 1.09 without administration of corticosteroids.

Meaning Administration of IL-6 antagonists, compared with usual care or placebo, was associated with lower 28-day all-cause mortality in patients hospitalized for COVID-19.

Any questions?

Further information

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