Tixagevimab–Cilgavimab EVUSHELD Intramuscular Pre-exposure Prophylaxis in High Risk COVID-19 Patients (PROVENT)

SUMMARY

n=5197 COVID-19 negative, high risk outpatients

EVUSHELD 300 mg
2 consecutive IM injections, 150mg each of tixagevimab and cilgavimab
(Note, dose studied differs from that currently used.)

vs

Placebo

Primary Endpoint Result:
Symptomatic COVID-19
RRR =77%; NNT=133 /at ~3 months
RRR =83%; NNT=68 /at ~6 months

Well tolerated with no statistically significant differences at 6 months in the number of participants experiencing any one adverse event, **EVUSHELD** 45.6% placebo 45.5% except for serious cardiac adverse events, **EVUSHELD** 0.7% placebo 0.3% **NNH=263**.

Concerns related to: efficacy vs current variants; safety (lack of long-term data, cardiovascular SAE), optimal dose, if repeat is required after 6-months, and overall value vs other options with better outcome data (hosp. & death).

Bottom line: In patients who have a contraindication to vaccines, or are immunocompromised/high risk, or are unvaccinated and at high risk of exposure to COVID-19, intramuscular administration of **EVUSHELD** COVID-19 **significantly reduced symptomatic COVID-19 infection at 6 months post-administration (NNT=68)**. Hospitalizations and death occurred too infrequently to determine if an effect was present. Real world efficacy is unknown.

TRIAL BACKGROUND

DESIGN: Randomized, multinational (87 sites, 5 countries), double-blind (participants, clinicians, outcome assessors until ~ 3 months then unblinding occurred) placebo-controlled trial. Sponsor involvement in trial design, data collection and analysis, various analysis of censored data once unblinding occurred, and patients opted to be vaccinated; trial was conducted between May-Nov 2021 (Alpha and Delta variants most prominent); follow-up at median of 83 and 196 days. Modified ITT analysis for the efficacy endpoint (3441 patients) excluded patients who did not have a prior confirmation of being COVID-19 negative (n=19); these patients were included in the safety analysis.

INTERVENTION: Tixagevimab 150 mg + cilgavimab 150 mg **EVUSHELD IM once** versus matching **placebo** in high risk COVID-19 negative patients

INCLUSION: ≥18 yrs of age, ↑ risk of an inadequate response to COVID-19 vaccination (e.g. ≥60 yrs of age, obese, CHF, COPD, CKD, chronic liver disease, immunocompromised, etc.), or intolerant to vaccines or at high risk of exposure (health care workers including staff working in long-term care facilities, workers in industrial settings such as meatpacking plants, military personnel, students living in dormitories, & others living together in close or high-density proximity or both), negative result from point of care COVID-19 serology testing at screening, medically stable & using contraception.

EXCLUSION: Significant infection or other acute illness, including fever (>37.8°C), a history of COVID-19 infection, positive COVID-19 result at screening, received a vaccine or biologic agent indicated for the prevention of COVID-19 infection, history of infection with severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS), bleeding disorder or prior history of significant bleeding or bruising following IM injections or venipuncture, any other significant disease, pregnant or breastfeeding, blood drawn in excess of a total of 450 mL (1 unit) for any reason within 30 days prior to randomization.

POPULATION: n=5197, average age 54yrs (43% of the participants were ≥60yrs), 46% ♀; global representation, 15% Hispanic/Latinx, 73% White, and 17% Black. Comorbidities: 42% obese, 78% have ≥1 risk factor (obesity, CKD, diabetes, immunosuppressed, CV disease, COPD, chronic liver disease, hypertension, asthma, cancer, smoking or sickle cell disease). 52.5% of patients had ↑ risk of exposure to COVID-19. Baseline demographics: well-balanced groups. Discontinued the study early (withdrawal, lost to follow-up, etc.), **EVUSHELD** 5% vs placebo 6%.

RESULTS — Follow-up @ 3- and 6-months post-dose

Primary Outcome	EVUSHELD n=3441	Placebo n=1731	Difference % 95% CI	Comments
Symptomatic RT-PCR positive COVID-19 **within ~3 months post-dose**	8 (0.2%)	17 (1.0%)	ARR = 0.7% 95% CI 46-90	↓ RR =77% **NNT=133** p<0.001 similar RR for unblinded data
Symptomatic RT-PCR positive COVID-19 **within ~6 months post-dose**	11 (0.3%)	31 (1.8%)	ARR = 1.5%	↓ RR =82% **NNT=68**; RR is 77% when the effect of unblinding is considered

RESULTS continued — Follow-up @ 3- and 6-months post-dose

Secondary Outcomes	EVUSHELD n=3441	Placebo n=1731	Difference % 95% CI	Comments
Severe or critical COVID-19 **within ~3 months post-dose**	0 (0%)	1 (0.1%)	NA	Events were too infrequent to determine if significant
Severe or critical COVID-19 **within ~6 months post-dose**	0 (0%)	5 (0.3%)	NA	
Emergency department visits for symptoms consistent with COVID-19	6 (0.2%)	0 (0%)	NA	3 out of 6 patients were positive for COVID-19 in the **EVUSHELD** group
Hospitalization **within ~6 months post-dose**	0 (0%)	7 (0.4%)	NA	
Death from any cause post-dose **within ~6 months post-dose**	9 (0.3%)	7 (0.4%)	NA	None of these deaths were considered to be related to the treatment

RESULTS continued			Follow-up @ 6-months post-dose
Harms – Safety Analysis	**EVUSHELD** n=3461	**Placebo** n=1763	**Difference**
Any adverse events (AE) (mild, moderate, severe)	1579 (45.6%)Mini	790 (45.5%)	↑ 0.1%
Participants with at least one serious adverse event	130 (3.8%)	58 (3.3%)	↑ 0.5%
Infections and infestations*	31 (0. 9%)	15 (0.9%)	n/a
Cardiac disorders**	23 (0. 7%)	5 (0.3%)	↑ 0.4% **NNH=263** (statistically significant for 1-sided t-test)
Nervous system disorders‡	18 (0.5%)	5 (0.3%)	↑ 0.2%

* Includes abdominal abscess, abscess limb, appendicitis, arteriovenous graft site infection, cellulitis, COVID-19, COVID-19 pneumonia, cystitis, device-related infection, diverticulitis, enterococcal bacteremia, gastroenteritis, influenza, localized infection, lower respiratory tract infection, lung abscess, osteomyelitis, peritonitis, pneumonia, postoperative wound infection, sepsis, septic shock, sialadenitis, soft tissue infection, staphylococcal infection, urinary tract infection, and urosepsis.
** Includes acute left ventricular failure, angina pectoris, arrhythmia, arteriosclerosis coronary artery, atrial fibrillation, cardiac failure, cardiomegaly, cardiomyopathy, cardio-respiratory arrest, congestive cardiac failure, coronary artery disease, myocardial infarction, and paroxysmal atrioventricular block.
‡Includes Bell's palsy, carotid artery stenosis, cerebral infarction, cerebrovascular accident, complex regional pain syndrome, dementia Alzheimer's type, dizziness, epilepsy, hepatic encephalopathy, lacunar infarction, loss of consciousness, metabolic encephalopathy, migraine, partial seizures, presyncope, ruptured cerebral aneurysm, seizure, syncope, and transient ischemic attack.

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:

- Global participation (Belgium, France, Spain, the United Kingdom, and the United States) should help for broader applicability.

LIMITATIONS:

- Several endpoints occurred too infrequently to determine statistical significance of any differences between groups, including severe or critical COVID-19, hospitalization, ER visits, or death from any cause.
- Secondary analysis included 0.5% (25/5197) of patients who had tested positive for COVID-19 at baseline (19 **EVUSHELD**, 6 placebo). These patients are at a lower hospitalization or death risk due to COVID-19.
- In the **PROVENT trial**, <2% of patients in the placebo group acquired COVID-19 compared to 6% in the **EPIC-HR trial**. Patients in the **PROVENT trial** may have been at a lower risk of contracting COVID-19.
- The hospitalization rate in the placebo group is 0.4% compared to 7% in the **EPIC-HR trial**. This difference in hospitalization rate may reflect that patients in the **PROVENT trial** had a lower risk of progressing to severe outcomes.
- Some populations are under-represented (e.g., African ancestry, Indigenous, immunocompromised patients (3.8%), and older adults).
- 22% of patients did not have a medical risk factor for progression to moderate/severe COVID-19.

UNCERTAINTIES

- Trial included a mix of vaccinated and unvaccinated patients after unblinding (42% **EVUSHELD**, 43% placebo). 34% of **EVUSHELD** and 49% of placebo participants were vaccinated after unblinding.
- Did unblinding impact trial participants' behaviours in a way that would affect their exposure to COVID-19?
- Did access to COVID-19 vaccines change during the trial reflecting participants' desire to get vaccinated? The effect of vaccination on progression to severe outcomes such as hospitalizations/death is unknown.
- Trial data represents a window of time where the Alpha and Delta variants would have been most prevalent. Is **EVUSHELD** effective against currently circulating COVID-19 subvariants e.g., Omicron?
- Is the primary endpoint of "symptomatic COVID-19" relevant vs. an endpoint such as hospitalizations and/or death?
- What is the quality of the immune response to vaccination after receiving **EVUSHELD**?
- Does use of EVUSHELD for prevention affect its potential efficacy for treatment?
- Would **EVUSHELD** still be effective in patients with a past history of COVID-19 infection (as is the case for many Canadians)?
- How many patients were COVID-19 positive but asymptomatic?
- Does **EVUSHELD** alter the efficacy or safety of other COVID-19 therapeutics such as **nirmatrelvir-ritonavir** or **remdesivir**?
- Does **EVUSHELD** exclude patients from receiving other COVID-19 therapeutics in certain jurisdictions (e.g., Saskatchewan)?
- Should repeat dosing be offered, and if so, at what interval?
- What is the optimal dose given current trend to use higher doses?

SHARED DECISION MAKING CONSIDERATIONS WHEN DECIDING TO OFFER PRE-EXPOSURE PROPHYLAXIS

- Patient values, risk of COVID-19, risk of progressing to severe outcomes, potential to benefit vs harms.

HEALTH SYSTEMS PERSPECTIVE WHEN CONSIDERING HOW TO OPERATIONALIZE ACCESS TO THIS THERAPY

- Health care worker fatigue, operational costs to implement, consideration of site type for access i.e. primary, secondary or tertiary care, other COVID-19 treatment options available, alignment with COVID-19 public health approaches, jurisdictional comparisons.

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References:

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2. FDA. FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR EVUSHELD (tixagevimab co-packaged with cilgavimab). 2022. Available from https://www.fda.gov/media/154701/download