Sotrovimab XEVUDY Single Infusion for Mild-Moderate COVID-19 Outpatients with 1+ Risk Factors (The COMET-ICE RCT – Prespecified Interim Analysis)[1]

SUMMARY

n=583 outpatients with mild-moderate COVID-19, at high risk of progression, & presenting ≤5 days of symptoms

Sotrovimab XEVUDY 500mg IV infusion x1 **vs** **Placebo**

Primary Endpoint Result:
Hospitalization >24hr for any cause or all-cause mortality by day 29:
↓RR ~85%; NNT≈17 /29d follow-up

n=868 for safety analysis; 24-week follow-up
Adverse events (AE) = 17% vs 19%
Serious AEs (SAE) = 2% vs 6%
(AE & SAE more common in placebo group)

Note: 1) no participants vaccinated, 2) protocol was adjusted to enrich the at-risk population (BMI & age), 3) no activity vs more recent BA.2 variant

Bottom line: Giving a **sotrovimab single infusion within 5 days of symptoms** reduced the risk of hospitalization or death in symptomatic COVID-19 adult outpatients at increased risk for COVID-19 progression to severe disease. **However, sotrovimab may lack activity versus the sub-variant (BA.2) and thus does not have a current role in COVID-19 therapy (USA and Canada).**[2,3]

TRIAL BACKGROUND {See additional information section at end of trial summary for full inclusion/exclusion criteria}

COMET-ICE = COVID-19 Monoclonal Antibody (mAb) Efficacy Trial-Intent to Care Early

HYPOTHESIS: this mAb targets a viral component thought to be conserved as new variants emerge; however resistance is still a concern

DESIGN: randomized, double-blind (participants, clinicians, outcome assessors), placebo-controlled trial; allocation concealed; patients stratified (by age ≤70 or >70, symptom duration ≤3 days or 4-5 days, and geographic region); ITT approaches used for efficacy endpoints. The trial was conducted in 37 trial sites in 4 countries (USA >90%, Canada, Brazil, Spain) between Aug 2020 – Mar 2021 (randomization up to Jan 19, 2021 for ITT efficacy population; Feb 17, 2021 for safety population). A prespecified interim analysis assessed safety and futility. This resulted in the trial being stopped early for benefit. Follow-up to continue. The trial was sponsored by industry who participated directly in the design, data collection, analysis, interpretation, and writing.

INTERVENTION: **sotrovimab 500mg XEVUDY 1-hour infusion** x1 versus **saline placebo** infusion x1 (initiated **≤5** days symptom onset)

INCLUSION, select: COVID-19 confirmed, symptomatic ≤5 days, non-hospitalized adults **at high-risk** (≥1 characteristic or condition) for progression to severe COVID-19, e.g. age ≥55, diabetes requiring medication, BMI >30, HF class II-IV, immunosuppressive disease or meds, corticosteroids, biologics, COPD, mod-severe asthma, CKD (eGFR <60mL/min). Due to time of enrolment, Aug 2020 - Jan 19, 2021, vaccines not available/patient population was **NOT vaccinated.**

EXCLUSION, select: previous severe COVID-19 (shortness of breath at rest, O_2 <94%, use of supplemental oxygen); likely to require hospitalization in next 24hrs, or die in next ≤7 days; receipt of any vaccine ≤48hrs prior to enrollment or COVID-19 vaccine at any point prior to randomization.

POPULATION n=583 (efficacy), median duration of follow-up ~72 days; n=868 (safety), median duration of follow-up ~56 days; median age = 53 (18-96), ≥ age 65 = 22%; ♂ ~46%; BMI ~32; global representation but mostly white 88% (63% Hispanic/Latinx); ~57% initiated ≤3 days of symptom onset.

Risk Factors: BMI >30 63%, Age ≥55 47%, diabetes 23%, mod-severe asthma 16%, COPD 4%, CKD <1%, HF <1%; 58% of patients had 1 risk factor (30% had 2, 11% had ≥3). Baseline demographics: prognostically well-balanced groups. **NOTE: protocol changed mid trial to enrich the population at high risk**, specifically increasing the **BMI requirement for obesity** (**>35kg/m²**) and requiring a **minimum number of patients >70 years of age** to (15%).

RESULTS

Outcomes - Efficacy analysis thru day 29	**Sotrovimab** n=291 efficacy n=430 safety	**Placebo** n=292 efficacy n=438 safety	**ARR Difference %;** **NNT or NNH; 95% CI** (if statistically significant)		**Comments**
1°: Hospitalization >24hr for any cause or death from any cause	3 1%	21 7%	-6%; **NNT≈17**; 95% CI 13-26		1° Outcome: ↓RR ~ 85%. Only hospitalization (not death) component of outcome significant. Most hospitalizations were COVID-19 related (most commonly pneumonia). The 1 death was in the placebo group, was in one of the 5 patients admitted to the ICU and was COVID-19 related. The patient declined intubation and subsequently died by day 29. One additional death took place after day 29 (on day 37) for a COVID-19 patient with pneumonia. 29-day case-fatality rate ~ 0.2%. Applicability to current context (Omicron strain & vaccinated population), uncertain.
- Hospitalization >24hr, any cause	3 1%	21 7%	-5.81% **NNT≈17**		
- Death, any cause	0 0%	1 <1%	Not statistically significant		
Emergency dept visit or hospitalization for any cause, or death from any cause	6 2%	28 10%	-7.5% **NNT≈13**; 95% CI 9-26		
Emerg dept visit without hosp, or hosp for <24hr for any cause	1%	2%			
Severe or critical progression	<1%	7%			
Admission to ICU, any cause	0	2%			
Harms – Safety Analysis 24 wks			**ARR**	**NNT**	
Adverse Events (AE)	16.9%	19.4%	-2.5%	**NNT≈40**	Most AE non-serious. AE, SAE: more common with placebo. No trends were noted in lab data.
AE – any, related to the drug	1.8%	1.8%			
- Diarrhea	1%	<1%			
Any infusion related reaction	1%	1%			
Serious Adverse Events (SAE)	1.6%	5.9%	-4.3%	**NNT≈24**	

Planned interim analysis: resulted in study being halted due to benefit, but ongoing analysis continues

Subgroup results of interest: not yet available

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:

- Clinical endpoints of the trial were strong (e.g. hospitalizations, emergency department visits, ICU admissions) as opposed to merely symptomatic COVID-19.
- Withdrawal from trial was low (4 in each group).
- Both efficacy and safety endpoints favoured treatment with sotrovimab.

LIMITATIONS:

- Monoclonal antibodies have varying activity versus different variants/sub-variants. This trial done prior to the Delta and Omicron variants (SARS-COV-2 early variants predominant at the time). **Sotrovimab currently thought to not have suitable activity versus the more recent BA.2 variant;** current guidelines suggest it does not have a role in the USA or Canada.[2,3] {Data limited (in vitro); role could re-emerge pending more data.}
- Severely immunocompromised patients, a higher risk group of particular interest, were excluded.
- Patients could receive other treatment at the discretion of their physicians as per their local standard of care.
- Missing progression status was imputed under a missing-at-random assumption with the use of multiple imputation (assumption could be incorrect).
- Additional exploratory analysis for benefit/harm outcomes has not been conducted as part of this interim analysis, but further analysis is ongoing.
    - Exploratory endpoints include impact on ventilator days, ICU and total hospital length of stay, non-respiratory complications, emerging viral resistance to mAb, viral load in nasal secretions and blood, health related quality of life and time away from work.
    - Unfortunately, we do not have any insights on the relative benefit in various subgroups, e.g. those over age 70, who were prioritized in the enriched protocol change after RCT already in progress. Presumably, the relative benefit compared to harm would be much greater in this population, but how much and whether there is adequate benefit in lower risk groups is not yet published.
- Trial was stopped early resulting in the potential to overestimate benefit and underestimate harms.
- Size of safety analysis population not large enough to observe a rare AE.

UNCERTAINTIES

- What difference in sotrovimab safety and efficacy would result from a baseline autologous antibody response (emerging immunity due to vaccination or previous infection)?
- Would the logistics of giving a monoclonal antibody infusion to everyone at risk provide value, or drain, available healthcare resources for COVID-19 treatment?
- Does it still work in a vaccinated patient population?
- Results driven by hospitalizations; does it also provide a mortality benefit?
- In vitro data suggests it lacks activity against specific Omicron variants; is this also true in the real world?
- What is the optimal dose? Could higher doses of the drug be efficacious? (Some jurisdictions have embraced using at higher doses for Omicron.)
- Would death have been impacted if the study went on longer?
- Are there any rare harms that could emerge if given on a population level (e.g. A larger number of real-world patients)?
- Might sotrovimab have any impact and role in preventing long COVID?

RXFILES RELATED LINKS:

COVID-19: Useful Links and Resources https://www.rxfiles.ca/RxFiles/uploads/documents/Covid19-Links.pdf
EPIC-HR Trial Summary: https://www.rxfiles.ca/rxfiles/uploads/documents/EPIC-HR-Nirmatrelvir-Ritonavir.pdf

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Abbreviations, select: ARR=absolute risk reduction CI=confidence interval mAb=monoclonal antibody NNH=number needed to harm NNT=number needed to treat RCT=randomized controlled trial RR=relative risk, SAE=serious adverse events
Ongoing RCTs: further analysis is coming for the **COMET-ICE** RCT.

References:

Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Early Treatment for Covid-19 with SARS-CoV-2 Neutralizing Antibody Sotrovimab. N Engl J Med. 2021;385(21):1941-1950. doi:10.1056/NEJMoa2107934. Protocol and Supplementary Appendix also available online.

2 Health Canada. Sotrovimab for Injection - Risk of Treatment Failure due to Circulation of SARS-CoV-2 Omicron BA.2 Subvariant. Accessed online 31 Oct 2022 at https://recalls-rappels.canada.ca/en/alert-recall/sotrovimab-injection-risk-treatment-failure-due-circulation-sars-cov-2-omicron-ba2

3 ASPR (Office of the Assistant Secretary for Preparedness and Response). Sotrovimab Update April 5 2022. Accessed online 31 May 2022 at https://aspr.hhs.gov/COVID-19/Therapeutics/Products/Sotrovimab/Pages/default.aspx)

Additional info:

Full inclusion criteria (from Protocol):

5.1. Inclusion Criteria
Participants are eligible to be included in the study only if all of the following criteria apply:
5.1.1. Age and Risk Factors
1. Participant must be aged 18 years or older AND at high risk of progression of COVID-19 based on presence of one or more of the following risk factors: diabetes (requiring medication), obesity (BMI>30), chronic kidney disease (i.e., eGFR <60 by MDRD), congestive heart failure (NYHA class II or more), chronic obstructive pulmonary disease (history of chronic bronchitis, chronic obstructive lung disease, or emphysema with dyspnea on physical exertion), and moderate to severe asthma (participant requires an inhaled steroid to control symptoms or has been prescribed a course of oral steroids in the past year)
OR
2. Participant ≥ 55 years old, irrespective of co-morbidities.
5.1.2. Type of Participant and Disease Characteristics
3. Participants who have a positive SARS-CoV-2 test result (by any validated test e.g. RT-PCR on any specimen type)
AND
Oxygen saturation ≥94% on room air
AND
Have COVID-19 defined by one or more of the following symptoms: fever, chills, cough, sore throat, malaise, headache, joint or muscle pain, change in smell or taste, vomiting, diarrhea, shortness of breath on exertion
AND
Less than or equal to 5 days from onset of symptoms
5.1.3. Sex and Contraceptive/Barrier Requirements
4. No gender restrictions
5. Female participants must meet and agree to abide by the following contraceptive criteria. Contraception use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:
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a. Is a woman of non-childbearing potential (WONCBP) as defined in Section 10.4.
OR
b. Is a WOCBP and using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Section 10.4 of the protocol during the study intervention period and for up to 24 weeks after the last dose of study intervention. The investigator should evaluate potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first dose of study intervention.
A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) before the first dose of study intervention.
See Section 8.3.7 Pregnancy Testing of the protocol.
– If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
– Additional requirements for pregnancy testing during and after study intervention are located in Section 1.3 of the protocol.
The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy
5.1.4. Informed Consent
6. Capable of giving signed informed consent as described in Section 10.1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
OR
If participants are not capable of giving written informed consent, alternative consent procedures will be followed as described.

Full exclusion criteria (from Protocol):

• Patients are excluded from the study if any of the following criteria apply:
Medical Conditions
• Currently hospitalized or judged by the investigator as likely to require hospitalization in the next 24 hours
• Symptoms consistent with severe Covid-19 as defined by shortness of breath at rest or respiratory distress or requiring supplemental oxygen
• Patients who, in the judgment of the investigator, are likely to die in the next 7 days
• Severely immunocompromised patients, including but not limited to cancer patients actively receiving immunosuppressive chemotherapy or immunotherapy, those with a solid organ transplant or allogeneic stem cell transplant within the last 3 months, or those having conditions requiring the use of systemic corticosteroids equivalent to ≥0.5 mg/kg of body weight per day of prednisone within 6 weeks of randomization
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o Change: this criterion has been modified from the original protocol to clarify the definition of “severely immunocompromised.” See the “Changes to Protocol/SAP” section for more information
• Known hypersensitivity to any constituent present in the investigational product
• Previous anaphylaxis or hypersensitivity to a monoclonal antibody
Prior/Concurrent Clinical Study Experience
• Enrollment in any investigational vaccine study within the last 180 days or any other investigational drug study within 30 days prior to day 1 or within five half-lives of the investigational compound, whichever is longer
• Enrollment in any trial of an investigational vaccine for SARS-CoV-2
Other Exclusions
• Receipt of any vaccine within 48 hours prior to enrollment. Receipt of a SARS-CoV-2 vaccine prior to randomization at any time point. Vaccination (including vaccination for SARS-CoV-2) will not be allowed for 4 weeks after dosing
o Change: modified this criterion to clarify restrictions around dosing with a SARS-CoV-2 vaccine. See the “Changes to Protocol/SAP” section for more information
• Receipt of convalescent plasma from a recovered Covid-19 patient or anti–SARS-CoV-2 monoclonal antibody within the last 3 months
• Patients who, in the judgment of the investigator, will be unlikely or unable to comply with the requirements of the protocol through day 29