Early Remdesivir VEKLURY to Prevent Progression to Severe COVID-19 in Outpatients (The PINETREE RCT)[1]

SUMMARY

n=562 unvaccinated, higher risk COVID-19 outpatients, presenting ≤7 days of symptoms

Remdesivir VEKLURY IV x 3 days
(200mg Day 1, 100mg Days 2-3)

vs

Placebo

Primary Endpoint Result:
COVID-19 hospitalization or all-cause mortality by day 28:
↓RR ~87%; NNT ≈ 22 /28d follow-up

Primary endpoint driven by COVID-19 hospitalization reduction;
there were no deaths in either arm

Serious AEs: 1.8% vs 6.7%
(more common in placebo group)
Adverse events: 42% vs 46%
<2% stopped due to adverse events

Bottom line: IV remdesivir **VEKLURY** initiated **within 7 days of symptoms** reduced the risk of hospitalization in unvaccinated, symptomatic COVID-19 outpatients at high risk for COVID-19 progression to severe disease. Safety demonstrated. Concerns: potential for antiviral resistance & IV administration.

***NOTE**: Extrapolation of data difficult due to current Omicron strain circulation and high levels of vaccination in the Canadian population.*

BACKGROUND

- Remdesivir **VEKLURY** is an antiviral that inhibits SARS-CoV-2 RNA polymerase.[2] It is available in Canada (since 2020) and is approved for the treatment of COVID-19 in: ❶ non-hospitalized adults with positive SARS-CoV-2 viral testing at high risk for progression to severe disease,[1] PINETREE ❷ hospitalized adults and adolescents (≥12yrs weighing ≥40kg) with pneumonia requiring oxygen.[3] ACTT-1
- Place in therapy for non-hospitalized adults with mild-moderate COVID-19 with high risk for progression to severe disease:[4-6]
  - NIH: 1st line **PAXLOVID**, strong recommendation 2nd line remdesivir **VEKLURY** (if **PAXLOVID** unavailable / contraindicated due to DI). moderate recommendation
  - IDSA: suggest remdesivir **VEKLURY** if initiated within 7 days of symptom onset. conditional recommendation, low certainty evidence
    - Choice of agent should be individualized, and there is no data for combo treatment in this setting.
  - Saskatchewan: when outside **PAXLOVID** 5 day window, may be eligible for remdesivir **VEKLURY** (up to 7 days since symptom onset).

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

DESIGN: randomized, double-blind (participants, clinicians, outcome assessors; however, sponsor unblinded throughout), multisite (64 sites, 4 countries), placebo-controlled trial. Allocation was concealed. Primary efficacy outcome analyzed via modified ITT (mITT) approach. The trial was conducted between Sept 2020 – April 2021 (Early variants most prominent) and stopped early due to decreasing SARS-CoV-2 infection incidence and ethical concerns regarding placebo therapy given increased access to treatments and increasing vaccination rates. Sponsor: Gilead Sciences. Primary outcome was modified from all hospitalizations to COVID-19 hospitalizations as per FDA recommendation.

INTERVENTION: Remdesivir VEKLURY IV x 3 days (200mg Day 1, then 100mg Day 2 & 3) initiated ≤**7 days** from symptom onset.

INCLUSION, select: confirmed, symptomatic ≤7 days, unvaccinated, non-hospitalized individuals ≥12 years with ≥1 risk factor for progression to hospitalization e.g. chronic lung disease, hypertension, cardiovascular disease, diabetes, BMI ≥30, immunocompromised, chronic kidney disease, cancer OR ≥60 years regardless of risk factors.

EXCLUSION, select: expected to receive hospital care, prior hospitalization for COVID-19, treatment with other agents with activity against SARS-CoV-2, use of hydroxychloroquine or chloroquine, ALT or AST ≥5 × ULN, creatinine clearance <30 mL/min, pregnancy/lactation, strong P-glycoprotein inducers (rifampin or herbal medication).

POPULATION n=562; Age: mean 50yrs, ≥60yrs ~30%, <18yrs ~1.5%; ♂ ~52%; mean BMI 31; Race: White ~80%, Hispanic/Latinx 42%, Black ~7.5%, USA resident ~95%; **Comorbidities:** diabetes ~62%, obesity ~55%, hypertension ~48%, chronic lung disease ~24%, CV/cerebrovascular disease ~8%, current cancer ~5%, immune compromise ~4%, CKD ~3%; **COVID-19 Characteristics:** median duration of symptoms prior to 1st infusion 5 days (IQR 3-6); median time since PCR confirmation 2 days (IQR 1-4), viral load ~6.3 $\log_{10}$ copies/mL.

RESULTS

follow-up: ~28 days after initiating treatment regimen

Efficacy Analysis	Remdesivir n=279	Placebo n=283	HR or RR (95% CI) NNT	Comments
1°: Hospitalization (COVID-19) or death from any cause, day 28	2 (0.7%)	15 (5.3%)	HR 0.13 (0.03 to 0.59) **NNT ≈ 22**	1° Outcome: ↓RR ~ 87%; p=0.008. Only one component of the composite i.e. hospitalization (COVID-19) was significant. All COVID-19 hospitalizations occurred by day 14. No deaths occurred by day 28. No significant difference in change in nasopharyngeal viral load from baseline to Day 7, HR 0.07 (-0.1 to 0.24). Median duration of symptoms before the first infusion was 5 days (IQR 3-6). Prespecified subgroup analyses: consistent lower incidence of the primary outcome in the remdesivir group, HR ranged from 0.11 to 0.17.
- Hospitalization (COVID-19)	2 (0.7%)	15 (5.3%)	HR 0.13 (0.03 to 0.59) **NNT ≈ 22**	
- Death, any cause	0	0	N/A	
Medical visit (COVID-19) or death from any cause, day 28	4/246 (1.6%)	21/252 (8.3%)	HR 0.19 (0.07 to 0.56) **NNT ≈ 15**	
Alleviation of symptoms by day 14 (FLU-PRO Plus questionnaire)	23/66 (34.8%)	15/60 (25%)	RR 1.41 (0.73 to 2.69)	
Hospitalization from any cause, day 28	5 (1.8%)	18 (6.4%)	HR 0.28 (0.1 to 0.75)* **NNT ≈ 22**	

*post-hoc

Safety Analysis	Remdesivir n=279	Placebo n=283	P value*	Comments
1°: Any Adverse Event	42.3%	46.3%	0.385	Numerically more AEs in the placebo group. Most common non-serious AE occurring ≥5% of individuals was nausea, headache, cough. Serious adverse events were more common with placebo. Authors did not report data on type of serious adverse event. Adverse events related to COVID-19 e.g. cough, dyspnea, chills, pyrexia were higher in the placebo group. Few patients (<2%) in either study arm discontinued trial due to adverse events. No remdesivir infusion reactions reported, but has been noted in the literature (frequency undefined). One death in placebo group at Day 59 (age 69, ♂, COVID-19 related hospitalization requiring ICU).
Serious Adverse Event	1.8%	6.7%	0.007 **NNT ≈ 20**	
Adverse event leading to discontinuation	0.7%	1.8%	0.458	
AE related to trial regimen	12.2%	8.8%	0.247	
Adverse Events				
- nausea	10.8%	7.4%	0.219	
- headache	5.7%	6%	0.966	
- cough	3.6%	6.4%	0.187	
- ageusia	2.9%	2.5%	0.978	
- anosmia	3.2%	2.1%	0.581	

*calculated by RxFiles

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS

- Overall robust study methodology e.g. randomized with allocation concealment, double-blind, and baseline demographics were well-balanced between groups. See limitations below regarding analysis and sponsor role.
- All patients in both study arms were accounted for. None were lost to follow-up.
- Primary composite outcome assessed was both objective and patient important.

LIMITATIONS

- The study was stopped early and underpowered (estimated sample size required 1264, and only 562 individuals or 45% were enrolled).
  - Study was stopped due to decreasing SARS-CoV-2 infection incidence and ethical concerns regarding placebo therapy given increased access to treatments and increasing vaccination rates.
  - Less exposure to remdesivir limits the ability to detect rare adverse events.
- The fragility index for the primary outcome was 4, meaning the result would no longer be significant if the primary end point occurred in 4 more patients in the remdesivir group.[7,8] 20 patients discontinued treatment early, which could impact results.
- Not true intention-to-treat analysis which is preferred in superiority trials. Instead, authors used a modified intention-to-treat analysis, which excluded 22 patients, n=13 remdesivir & n=9 placebo, who were randomized but did not receive an infusion. Potential to impact results as small number of events occurred during the trial.
- Remdesivir significantly reduced the primary composite outcome, but only reduced COVID-19 hospitalizations. No impact on mortality. Other agents, such as nirmatrelvir/ritonavir **PAXLOVID** have shown a reduction in both COVID-19 hospitalizations and mortality.
- Individuals were enrolled from 4 countries – US, Spain, Denmark, UK – and the majority where White or Hispanic/Latinx. <10% of individuals self-reported as Black or Indigenous which is an important population as these groups are at increased risk for COVID-19 due to systemic health and social inequalities.
- Remdesivir is administered as an infusion (over 30 mins, up to 120 mins) and requires specialized equipment, healthcare personnel, monitoring throughout and post infusion (1 hour).[9] Remdesivir has been associated with infusion-related reactions, although none were reported in this study.
- Sponsor was unblinded throughout and was intimately involved with the trial e.g. responsible for: collecting data, monitoring trial conduct, performing statistical analysis, and preparing the manuscript.

UNCERTAINTIES

- Would remdesivir show a mortality benefit if the study had continued and more patients enrolled?
- Does remdesivir provide the same results in adolescents? **PINETREE** enrolled only 8 individuals (1.8%) <18 years. In Canada, only approved for non-hospitalized patients 18 years or older and hospitalized patients 12 years or older weighing 40kg or more.
- Would there be potential for benefit if initiated >7 days post-symptom onset?
- Would remdesivir have the same efficacy against other COVID-19 strains?
- Does remdesivir impact other patient important outcomes e.g. long-COVID or other complications?
- Does remdesivir impact viral transmission? Potential for COVID-19 transmission as multiple sources of contact with healthcare personnel for remdesivir administration.
- How would remdesivir be administered with limited system resources?
- Trial studied non-vaccinated. Would it be effective in those who are partially vaccinated, or fully vaccinated?
- Would there be relative benefit over harm in lower risk (e.g. vaccinated, previously infected) patients? Should it be given a role in lower-risk patients?
- What is the benefit/safety in those with renal impairment (eGFR <30mL/min) who were excluded from the trial? Would a lower dose be safe/effective?

RXFILES RELATED LINKS:

- **TRIAL SUMMARY EPIC-HR RCT:** https://www.rxfiles.ca/RxFiles/uploads/documents/EPIC-HR-Nirmatrelvir-Ritonavir.pdf

ACKNOWLEDGEMENTS: Written by Marlys LeBras. Thanks to our Trial Summary Reviewers: L Regier, A Crawley, J Bareham, A Soubolsky, T McAleer, S Duggal, S Lee (Inf Disease), D Lamb, C Bell, K Boechler

Abbreviations, select: **AE**=adverse events **CI**=confidence interval **HR**=hazard ratio **IDSA**=Infectious Diseases Society of America **ITT**=intention to treat **IQR**=interquartile range **NIH**=National Institutes of Health **NNT**=number needed to treat **RCT**=randomized controlled trial **RR**=rate ratio or relative risk

References:

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6. MedSask Mild COVID-19 Infection Guidelines. Available at: https://medsask.usask.ca/professional-practice/paxlovid-hcp/prescribing-paxlovid-for-covid-19.php. Accessed [June 7, 2022].
7. Letter to the editor. Pierre-Vladimir Ennezat. Feb 16, 2022. DOI: 10.1056/NEJMc2200591.
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Additional info:

Full inclusion criteria (from Protocol):

Participants must meet all of the following inclusion criteria to be eligible for participation in this study:

1) **Age 18 years or older with at least 1 of the following pre-existing risk factors for progression to hospitalization:**
   a) Chronic lung disease: chronic obstructive pulmonary disease, moderate-to-severe asthma, cystic fibrosis, pulmonary fibrosis
   b) Hypertension: systemic or pulmonary
   c) Cardiovascular or cerebrovascular disease: coronary artery disease, congenital heart disease, heart failure, cardiomyopathy, history of stroke
   d) Diabetes mellitus: Type 1 or 2
   e) Obesity (BMI ≥30)
   f) Immunocompromised state
   g) Chronic kidney disease: any stage
   h) Chronic liver disease
   i) Current cancer
   j) Sickle cell disease

OR

Age **60 year or older, regardless of the presence of other pre-existing risk factors for progression**

2) SARS-CoV-2 infection confirmed by **PCR ≤ 4 days prior to screening**
4) ≥1 symptom(s) consistent with COVID-19 for ≤ 7 days prior to randomization e.g. fever, cough, fatigue, SOB, sore throat, headache, myalgia/arthralgia)
5) Oxygen saturation (SpO2) > 94% on room air
6) Not currently requiring hospitalization
7) Participants of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception

Full exclusion criteria (from Protocol):

Participants who meet *any* of the following exclusion criteria are not eligible to be enrolled in this study:

1) Participation in any other clinical trial of an experimental treatment and prevention for COVID-19
2) **Prior hospitalization** for COVID-19
3) Treatment with other agents with actual or possible direct antiviral activity against SARS-CoV-2
4) Use of **hydroxychloroquine or chloroquine** ≤ 7 days prior to screening
5) Requiring oxygen supplementation
6) **ALT or AST ≥ 5 × ULN** at screening or within 90 days of screening
7) **Creatinine clearance < 30 mL/min** at screening or < 90 days before screening ONLY if the participant's weight is < 48 kg
8) Breastfeeding female
9) Known hypersensitivity to the study drug, the metabolites, or formulation excipient
10) Use or planned use of exclusionary medications: investigational or approved agents for the SARS-CoV-2 virus including approved HIV protease inhibitors such as lopinavir/ritonavir, interferon, etc; hydroxychloroquine or chloroquine, strong inducers of P-glycoprotein (rifampin or herbal medication)