Nirmatrelvir and ritonavir (NMV-r; Paxlovid\textsuperscript{TM}) is an oral antiviral drug combination that targets a key SARS-CoV-2 protease enzyme. It was approved by Health Canada on January 17, 2022 for treatment of mild-to-moderate Covid-19 disease in adult patients at high risk for progression to hospitalization or death. The initial US cost was US\$529/person; the Canadian negotiated price is secret.\textsuperscript{1} This Letter presents highlights of the Therapeutics Initiative (TI) interim post-market analysis of NMV-r prescriptions in British Columbia (BC). We plan final analyses for later in 2023.

Why study real-world use of NMV-r?
Health Canada approved NMV-r based on interim efficacy and safety data from the Evaluation of Inhibition for Covid-19 in High-Risk Patients trial (EPIC-HR).\textsuperscript{2,3} This double-blind, randomized, placebo-controlled trial (DBRCT) was designed and conducted by Pfizer and ICON between July 16 and December 9, 2021 in 20 countries (5 continents).\textsuperscript{4} For the primary endpoint, in 2,246 patients not vaccinated against Covid-19, but randomized within 5 days of symptom onset, NMV-r reduced Covid-19-related hospitalization or death from any cause by Day 28 by 5.6% absolute (88% relative) risk, compared with placebo. By Day 28 there were no deaths in the NMV-r group vs 12 in the placebo group (no claim for statistical significance). EPIC-HR reported numerically fewer serious adverse events (SAEs) but more suspected drug-related AEs from NMV-r than from placebo.

From August to December 2021 Pfizer enrolled patients in a second DBRCT of NMV-r (EPIC-SR) in lower-risk adults (called “standard-risk”). After randomizing 1,141 participants (20 countries), it announced closure of the trial in a June 14, 2022 media release, “due to a very low rate of hospitalization or death observed in the standard-risk patient population.”\textsuperscript{5} The media release indicated that NMV-r was not effective to reduce symptoms (the primary endpoint). It reported a non-statistically significant, 0.9% absolute (5% relative) risk reduction in a secondary endpoint of hospitalization or death. Pfizer indicated its intention to publish EPIC-SR results, but this is yet to occur; it has not posted results at clinicaltrials.gov, or on its website.\textsuperscript{6,7}

The benefit-harm profile of NMV-r in the BC population taking this drug combination is unknown. Like most provinces in Canada, BC adopted eligibility criteria for NMV-r that differ substantially from participants in the EPIC-HR trial. Unlike our BC population, patients enrolled in EPIC-HR were unvaccinated and had no natural immunity from prior Covid-19 infection. They were infected by Covid-19 variants different from those now circulating in Canada. EPIC-HR also excluded people who were taking drugs with known CYP 3A4 interactions.\textsuperscript{8}

Who can access NMV-r in BC?
Four groups of patients are currently eligible. Three consist of “clinically extremely vulnerable” (CEV) individuals with medical conditions previously designated by a group of BC specialists in order to prioritize Covid-19 vaccinations. Two include people 12 years and older who are severely (CEV1) or moderately (CEV2) immunocompromised. CEV3 individuals are not immunocompromised, but have medical conditions that engender a high risk for complications from Covid-19. A fourth Expanded Eligibility group was added March 17, 2022 to allow wider access to NMV-r. Eligibility criteria for NMV-r in BC are available online.\textsuperscript{9}

Preliminary TI analysis of NMV-r in BC
As in the EPIC-HR trial, the TI Pharmacoepidemiology group is analyzing the 28-day risk of Covid-19-related hospitalization or death from any cause in the groups eligible for treatment in BC. To minimize confounding bias, we limit the analysis to the subset of individuals to whom NMV-r was dispensed (“index cases”), and for whom we can match a person (control) of the same age (+2 years), sex, and with laboratory-confirmed Covid-19 infection within a month of the paired index case. We also match for propensity scores, a common pharmacoepidemiologic method to control for imbalances between groups in comorbidities.

We use Ministry of Health datasets including PharmaNet, hospital discharge abstracts, emergency department encounters, physician office billing diagnostic codes, Covid-19 PCR testing, and Covid-19 vaccination status. The study has ethics approval from the University of British Columbia and our methods guarantee protection of the privacy of patients, prescribers, and dispensing pharmacists.

We are also assessing patient follow-up data collected by community pharmacists as part of the Paxlovid\textsuperscript{TM} Follow-up initiative (PAX-F) implemented by the Ministry of Health when NMV-r became available.\textsuperscript{10} Pharmacists phoned patients or their caregivers 6 to 10 days after dispensing NMV-r. They asked about treatment completion, adverse drug events (ADEs) and their management, and recorded adherence and ADE information in PharmaNet.
Several BC experts reviewed the draft of this Therapeutics Letter for factual accuracy, and to ensure it is relevant to clinicians. The UBC TI is funded by the BC Ministry of Health to provide evidence-based information about drug therapy. We neither formulate nor adjudicate provincial drug policies.

### NMV-r effectiveness in BC

The results shown here are early findings for patients with a positive PCR test who were eligible for NMV-r between February and September 2022. These analyses are yet to be peer reviewed. Our preliminary analysis relies on emergency department (ED) visit records from the National Ambulatory Care Reporting System (NACRS), because hospital discharge data will not be available until later in 2023. We counted people with an ED visit record indicating Covid-19 infection and admission to hospital as having been hospitalized for Covid-19. For this interim analysis, the ED visit data provide a reasonable proxy for more complete hospital records. The Table shows interim results. Compared with controls (no NMV-r), treatment with NMV-r was associated with statistically significant relative reductions in the composite outcome of about 80% in the CEV1 and CEV3 groups. We found a non-significant 41% reduction in the matched CEV2 group, and a non-significant increased risk in the Expanded Eligibility group. Among BC residents, the Expanded Eligibility group’s experience is the most relevant to clinicians and policy makers contemplating broader availability of NMV-r. This group had the lowest background risk of the composite endpoint: 1% in untreated matched controls. It is the closest comparator to “standard-risk” participants in the unpublished EPIC-SR trial. Similar to EPIC-SR, the results in this BC cohort do not yet show a benefit of treatment on Covid-19-related hospitalization or death from any cause.

### Harms of NMV-r in BC

The principal concern is from pharmacokinetic (PK) drug interactions caused by ritonavir, the potent inhibitor of cytochrome P450 3A – used as a sort of “controlled grapefruit juice” to increase bioavailability of nirmatrelvir. Follow-up data collected by 1,962 BC pharmacists between February and December 2022 as part of PAX-F shows that 10,200 patients who received 10,356 courses of NMV-r were asked about their adherence to therapy and adverse drug events (ADEs). Of respondents, 88% reported completing the 5-day course. The remaining 12% reported partial completion: 4.2% discontinued due to a suspected ADE; 4% took no medication after accepting dispensing; for 2% treatment adherence was not recorded.

We also analyzed the PharmaNet database for drugs known to interact with NMV-r. Of 18,035 individuals dispensed NMV-r in 2022, we estimate that 11,050 (61%) had a previously dispensed and available supply of a drug with potential for PK interactions, when they received NMV-r. Nearly all such potential interactions were seen as manageable by the prescriber. In future we may be able to quantify some management strategies implemented, such as drug switches, suspensions, or dose decreases.

### Conclusions

- Efficacy evidence for NMV-r (Paxlovid™) derived from unvaccinated high-risk patients in 2021 may be irrelevant to BC patients in 2023. In lower-risk patients, benefits have not been proven.
- We found evidence suggesting some benefit in defined high-risk groups in BC during 2022.
- PharmaCare’s temporary initiative to record adverse drug events may lead to better ways to document them in future.

#### Table: Covid-19-related emergency hospitalization or death by Day 28 after treatment initiation in EPIC-HR trial vs British Columbia

<table>
<thead>
<tr>
<th></th>
<th>EPIC-HR trial</th>
<th>CEVI Cohort</th>
<th>CEV2 Cohort</th>
<th>CEV3 Cohort</th>
<th>Expanded Cohort</th>
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<tr>
<td>NMV-r treated</td>
<td>N = 1039</td>
<td>N = 263</td>
<td>N = 1204</td>
<td>N = 967</td>
<td>N = 640</td>
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<td>Events (%)</td>
<td>8 (0.8)</td>
<td>masked*</td>
<td>16 (1.3)</td>
<td>masked*</td>
<td>12 (1.9)</td>
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<td>Control</td>
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<td>N = 263</td>
<td>N = 1204</td>
<td>N = 967</td>
<td>N = 640</td>
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<tr>
<td>Events (%)</td>
<td>66 (6.3)</td>
<td>masked*</td>
<td>27 (2.2)</td>
<td>masked*</td>
<td>7 (1.1)</td>
</tr>
<tr>
<td>Adjusted RR (95% CI)</td>
<td>0.12 (0.06-0.25)</td>
<td>0.18 (0.04-0.80)</td>
<td>0.59 (0.32-1.10)</td>
<td>0.22 (0.07-0.65)</td>
<td>1.70 (0.68-4.40)</td>
</tr>
</tbody>
</table>

* Masked numbers are too small to report because of data privacy requirements.

#### References