

CADTH Reimbursement Recommendation

Risperidone for Extended-Release Injectable Suspension (Perseris)

Indication: For the treatment of schizophrenia in adults

Sponsor: HLS Therapeutics Inc.

Final recommendation: Reimburse with conditions

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

What Is the CADTH Reimbursement Recommendation for Perseris?

CADTH recommends that Perseris should be reimbursed by public drug plans for the treatment of schizophrenia in adults if certain conditions are met.

Which Patients Are Eligible for Coverage?

Perseris should be covered by public drug plans in a similar manner to other long-acting injectable atypical antipsychotic drugs for the treatment of adults with schizophrenia.

What Are the Conditions for Reimbursement?

Perseris should only be reimbursed if the total monthly dose is not more than 120 mg and is not used in combination with other long-acting injectable antipsychotic drugs. Perseris should not cost more than other long-acting injectable (LAI) atypical antipsychotic drugs.

Why Did CADTH Make This Recommendation?

- One clinical trial showed that treatment with Perseris improved symptoms of schizophrenia in adult patients compared with placebo, as measured by the Positive and Negative Syndrome Scale and Clinical Global Impressions-Severity.
- No evidence reviewed suggests Perseris is more effective than other similar reimbursed therapies used to treat adults with schizophrenia. Therefore, Perseris should cost no more than the lowest cost alternative long-acting injectable atypical antipsychotic drug to ensure cost-effectiveness.
- Based on public list prices, the 3-year budget savings is \$298,205.

Additional Information

What Is Schizophrenia?

Schizophrenia is a severe and chronic psychiatric disease that may vary in presentation, course, treatment response, and outcome. Symptoms of schizophrenia may include hallucinations, delusions, cognitive impairment, disorganized thoughts, social withdrawal, and lack of motivation. The incidence of schizophrenia in Canada has been estimated to be approximately 49 per 100,000 in 2016, with 58 per 100,000 in male and 41 per 100,000 in female.

Unmet Needs in Schizophrenia

All LAI atypical antipsychotic drugs currently available for the treatment of schizophrenia are administered intramuscularly (IM) and require oral supplementation or loading doses given either the same day or requiring additional office visits. There is a need for more convenient LAI antipsychotic drugs with simpler administration.

How Much Does Perseris Cost?

Treatment with Perseris is expected to cost approximately \$5,474 to \$7,299 per patient annually.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that risperidone for extended-release injectable suspension (90 mg or 120 mg subcutaneous injection) should be reimbursed for the treatment of schizophrenia in adults only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, randomized, double-blind, placebo-controlled study (Study 09-0010) evaluated risperidone extended release (ER), 90 mg and 120 mg, compared with placebo in patients aged 18 to 55 years with moderate-to-severe schizophrenia in an acute exacerbation phase (N = 354). Compared with placebo, both risperidone ER 90 mg and risperidone ER 120 mg demonstrated a statistically significant improvement in the primary outcome of Positive and Negative Syndrome Scale (PANSS) change from baseline (least square mean difference [LSMD], -6.15, 95% CI, -9.98 to -2.31, P = 0.0004 for risperidone ER 90 mg and LSMD, -7.24, 95% CI, -11.05 to -3.43, P < 0.0001 for risperidone ER 120 mg). Risperidone ER 90 mg and ER 120 mg also demonstrated a statistically significant improvement over placebo in the secondary outcome of Clinical Global Impressions-Severity (LSMD, -0.35, 95% CI, -0.56 to -0.14, P = 0.0002 for risperidone ER 90 mg and LSMD, -0.40, 95% CI, -0.60 to -0.19, P < 0.0001 for risperidone ER 120 mg). Patient group input described successful treatments as those that allow for the highest level of daily functioning, have minimal adverse events, and promote adherence. Patients also see that their symptoms have a significant impact on day-to-day functioning and, as such, the primary and secondary outcome results from the trial align with patient expectations.

Using the sponsor-submitted price for risperidone ER and publicly listed prices for all other comparable antipsychotic drug costs, risperidone ER was more costly compared with some other long-acting injectable (LAI) atypical antipsychotic [drugs] (AAPs), and risperidone ER is assumed to be similarly effective as other LAI AAPs. As such, risperidone ER should be no more costly than the least costly reimbursed LAI AAP for adults with schizophrenia.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason
Initiation	
1. Reimburse in a similar manner to other long-acting injectable atypical antipsychotic agents for the treatment of adults with schizophrenia.	There are no clinical data to support a clinical benefit for risperidone ER SC given monthly compared with other atypical long-acting injectable antipsychotic drugs.
Prescribing	
2. Monthly dose should not exceed 120 mg SC. 3. Risperidone ER should not be used in combination with other antipsychotic LAIs.	A dose of 120 mg SC monthly is the maximum Health Canada-approved dose. There is a lack of evidence to support using risperidone ER long-acting injectable in combination with other antipsychotic long-acting injectables.

Reimbursement condition	Reason
Pricing	
<p>4. The drug plan cost of treatment with risperidone ER should not exceed the least costly long-acting injectable atypical antipsychotic drug reimbursed for the treatment of schizophrenia.</p>	<p>At the submitted price, risperidone ER is more costly than some other atypical antipsychotic long-acting injectable antipsychotic drugs (especially at the higher dosing regimens).</p> <p>There is insufficient evidence to justify a cost premium for risperidone ER over the least expensive long-acting injectable atypical antipsychotic drug reimbursed for schizophrenia.</p>

ER = extended release; SC = subcutaneous.

Implementation Guidance

1. Prescribing conditions should be comparable to other atypical LAIs that are already being reimbursed for the treatment of moderate-to-severe schizophrenia.
2. Study 09-0010 enrolled patients with acute exacerbations of schizophrenia. In clinical practice, risperidone ER is also expected to be used for chronic disease management.
3. There is uncertainty in the negotiated prices of other LAIs that are reimbursed by drug plans. As such, the estimates of reductions in price may need to be adjusted to reflect the actual costs.

Discussion Points

- Risperidone, in various formulations, has been available for the treatment of schizophrenia in Canada for over 2 decades, with considerable clinical experience gained using this drug.
- The clinical expert consulted on this review has indicated that the efficacy of risperidone ER is expected to be similar to other atypical LAI antipsychotic drugs.
- CDEC noted that a longer duration of trials of risperidone ER compared with existing available oral risperidone or atypical antipsychotic LAIs in Canada for the maintenance treatment of schizophrenia are needed to adequately assess long-term outcomes including mortality, relapse, remission, and hospitalization.
- CDEC discussed the lack of clear results that reflect the important outcomes identified by the patient group. While the study demonstrated a statistically significant improvement over placebo in the secondary outcome of Clinical Global Impressions-Severity, the magnitude of change in this outcome did not meet the minimum important difference. Moreover, health-related quality of life and other patient reported outcomes were assessed as exploratory outcomes only. Thus, no conclusions could be made on these measures.
- Other formulations of risperidone are currently approved in Canada, including a tablet for once daily oral administration and a LAI formulation for IM administration every 2 weeks. Currently, the reimbursement status of risperidone LAI varies between the public drug plans.
- Other existing LAIs for schizophrenia are administered IM and require oral supplementation or loading doses given either the same day or requiring additional office visits. The sponsor

indicated that risperidone ER reached therapeutically relevant plasma concentrations on the first day of dosing, required no loading dose or supplemental oral risperidone dosing. Risperidone ER is administered subcutaneously, which may cause less pain than IM, although no evidence addressing this issue was provided in the sponsor's summary of clinical evidence for this review.

- No direct or indirect evidence was available comparing risperidone ER with any other antipsychotic medication used in the treatment of schizophrenia including risperidone tablet for once daily oral administration or LAI formulation for IM administration every 2 weeks.
- If a generic version of risperidone ER becomes available, the relative cost may be affected.

Background

Risperidone for ER injectable suspension, powder for suspension, 90 mg or 120 mg subcutaneous injection (risperidone ER) was approved by Health Canada in November 2020. It is indicated for the treatment of schizophrenia in adults. Like other AAPs, the exact mechanism of risperidone ER is unclear. The Health Canada recommended dose is 90 mg or 120 mg once monthly by subcutaneous injection. It does not require a loading dose. Risperidone ER 90 mg corresponds to 3 mg/day oral risperidone and risperidone ER 120 mg corresponds to 4 mg/day oral risperidone respectively.

Sources of Information Used by the Committee

CDEC considered the following information to make its recommendation:

- A review of 1 phase III, randomized, double-blind, placebo-controlled study in patients 18 to 55 years old with moderate-to-severe schizophrenia in an acute exacerbation phase.
- Patients perspectives gathered by 1 patient group, Institute for Advancements in Mental Health.
- Input from public drug plans that participate in the CADTH review process.
- One clinical specialist with expertise in diagnosing and treating patients with schizophrenia.
- A review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

The information in this section is a summary of the input provided by the patient groups who responded to CADTH's call for patient input and from the clinical expert consulted by CADTH for the purpose of this review.

Patient Input

- Patient group input was provided by the Institute for Advancements in Mental Health (IAM) and was obtained based on IAM's 40-year history of serving adults with schizophrenia. Their submission also draws some information from a survey of IAM's client network conducted in 2018. Respondents to this survey self-described as: 12% personally diagnosed, 50% caregiver, 63% family member or friend of someone diagnosed, and 18% work in social services.
- Respondents indicated that many of the patients experience symptoms of psychosis, which have a significant impact on day-to-day functioning. The patient's experiences vary widely but typically involve some levels of cognitive impairment, delusions, and hallucinations. A large number of patients also experience a lack of insight into their illness, which often has an impact on their ability and motivation to access treatment and supports. This symptom can cause significant strain in relationships, including those with caregivers and family members, ultimately leading to social isolation and a lack of supports for the individual with the illness.
- Patients indicated the most common side effects of antipsychotic drugs were drowsiness, dry mouth, restlessness, dizziness, muscle stiffness, constipation, and anxiety.
- Of the patients, 23% identified the cost of medications as a significant challenge to access; 63% indicated that it is difficult to pay for health care bills including medication, visits to specialists, and counselling; and 20% patients noted that identified the preferred medication not being covered by public drug programs is a challenge.
- Patients expect new, quick, simple, convenient, and affordable access to a wide range of treatments and medications to suit their unique needs, which can improve adherence and allows for the highest level of daily functioning and symptom reduction while managing side effects.

Clinician Input

Input From the Clinical Expert Consulted by CADTH

- The clinical expert indicated that current treatments do not treat the underlying pathophysiology, which is not really understood. Medications have burdensome side effects, which in some cases are life threatening (diabetes, neuroleptic malignant syndrome) or irreversible (tardive dyskinesia). Antipsychotic drugs treat only 1 of 3 symptom domains – they do not treat negative and cognitive symptoms. Treatments for refractory disorders are few and have severe side effects and are inconvenient.
- The clinical expert consulted by CADTH for this review anticipated that risperidone ER would initially be used as second-line treatment; it is a convenient LAI that does not require concomitant oral medication to initiate. This may allow for earlier hospital discharge or easier community initiation. Since it is based on a familiar drug, clinicians could be quick to adopt it.
- The clinical expert indicated that adult patients with well-diagnosed schizophrenia or schizoaffective disorder who have responded to oral risperidone would be the ideal candidates for risperidone ER. Geriatric and pediatric patients would not be good candidates given the lack of data in these groups and the risk of stroke and increased mortality in older adults. Patients with appropriately diagnosed treatment-resistant illness would be unlikely to benefit.
- The clinical expert indicated that a 20% reduction of positive symptoms on a valid psychosis rating scale, for example Positive and Negative Syndrome Scale (PANSS) or Brief

Psychiatric Rating Scale, is the most reliable way to confirm response to antipsychotic medication. However, such scales are often not used in clinical practice. Therefore, the routine mental status exam which thoroughly assesses hallucination, delusions and disorganized thought and behaviour is appropriate. Clinically meaningful improvement was usually defined as a 20% reduction of positive symptoms on a valid psychosis rating scale (e.g., PANSS). In addition, it would also involve improved function as manifested by more appropriate social interactions, greater consistency in activities of daily living, and reduction in risk for self-harm or aggression.

- The clinical expert indicated that in the acute phase in community, treatment response should be assessed at least twice a week, which can be done by in person or virtual visits, and collateral input. If in hospital, if the patient is at risk of aggression or suicide, daily assessment by physician or nurse is necessary. Once a patient is in the stabilization phase, in community, assessment once every week or two is adequate. In the maintenance phase, once a month or even once every 3 months can be adequate.
- The clinical expert indicated that if a patient has been symptom-free and had good functional recovery for 2 or more years, discontinuation can be considered.
- The clinical expert indicated that risperidone ER could be initiated in hospital or in the community, typically in an acute psychiatry unit, or a community or tertiary mental health program. Family physicians who are familiar with antipsychotic medication could also initiate it for patients with mild exacerbations who have demonstrated tolerability to risperidone oral medication.

Clinician Group Input

No clinician group input was received for this review.

Drug Program Input

Drug programs identified several key issues related to implementation as follows:

- The drug programs requested clarification on whether risperidone ER would be used for a patient who failed oral therapy or conventional LAIs. The clinical experts consulted by CADTH for this review indicated that risperidone ER should be offered to any patient who might benefit from the drug, not only those who fail oral therapy due to nonadherence.
- The drug programs asked whether there are special concerns with the use of risperidone ER (use of the Atrigel delivery system) in pregnant patients. The clinical expert indicated that risperidone ER has not undergone adequate study in pregnant women to determine that it is safe especially in the first trimester of pregnancy. The benefits may outweigh risks of risperidone ER for certain patients, and close monitoring would be necessary were it prescribed to a pregnant patient.
- The drug programs wondered if a washout period for patients currently on oral therapies would be required. The clinical expert indicated that patients who undergo a switch of antipsychotic usually have a “cross taper” in which the first medication is gradually reduced and discontinued over several weeks while the second is gradually increased. Although a washout period is not typically necessary for oral medications, a cross taper approach with this injection technology has not been studied.
- The drug programs requested clarification on whether risperidone ER would be used for prevention of relapse/maintenance. The clinical expert indicated that risperidone ER was shown in the regulatory trial to be effective for acute exacerbation of schizophrenia. Given experience with other risperidone and paliperidone LAIs, it is justified to assume that

risperidone ER will be effective for maintenance therapy, but a long-term study is required to confirm this.

- The drug programs requested clarification of the definitions of the “treatment resistant” or “refractory” disease. The clinical expert indicated that treatment-resistant schizophrenia is diagnosed in patients who do not have a response of at least 20% reduction in positive symptoms to either of 2 medication trials of different antipsychotic drugs at adequate dose and duration. These patients should receive clozapine whenever possible. A minority of patients also fail to meet response criteria for clozapine, and those patients are considered refractory.

Clinical Evidence

Pivotal Studies

Description of Studies Submitted by the Sponsor

The CADTH clinical review was based on a summary of clinical evidence provided by the sponsor in accordance with the CADTH tailored review process. One phase III, randomized, double-blind, placebo-controlled study (Study 09-0010), performed at 33 centres in the US, was included in the sponsor’s summary of the clinical evidence. The objective of Study 09-0010 was to evaluate the efficacy and the safety of risperidone ER compared with placebo in patients (N = 354) in patients 18 to 55 years old with moderate-to-severe schizophrenia in an acute exacerbation phase. The study was conducted on an inpatient basis in a hospital setting. Patients were randomized to 1 of 3 treatment groups: risperidone ER 90 mg subcutaneously, risperidone ER 120 mg subcutaneously, or placebo injection subcutaneously for 8 weeks. The primary outcome was the change from baseline in PANSS total score at end of treatment and the secondary outcome was change from baseline to end of treatment on the CGI-S.

Baseline demographic characteristics were generally balanced across treatment arms. The majority of patients included in the study were black (> 70%) and male (> 73.5%). The mean age ranged from 40.5 to 42.4 years across the 3 groups. The baseline disease characteristics were not summarized in the sponsor’s summary of clinical evidence.

Efficacy Results

The PANSS total score change from baseline at week 8 (primary outcome) demonstrated an improvement in risperidone ER 90 mg, risperidone 120 mg group, and placebo group (least square mean [LSM]: -15.37 [SE: 1.22], -16.46 [SE: 1.20], and -9.22 [SE: 1.22] in risperidone ER 90 mg, risperidone ER 120 mg, and placebo groups, respectively). Compared with placebo, both risperidone ER 90 mg and risperidone ER 120 mg demonstrated a statistically significant improvement (risperidone ER minus placebo, LSM difference [LSMD], -6.15, 95% CI, -9.98 to -2.31, P = 0.0004 for risperidone ER 90 mg and LSMD, -7.24, 95% CI, -11.05 to -3.43, P < 0.0001 for risperidone ER 120 mg). It is uncertain if the difference between risperidone ER treatment group and placebo were clinically meaningful. The CADTH clinical expert consulted for this review indicated that a 20% improvement of PANSS total score, is usually considered as a clinical meaningful response to the treatment in schizophrenia patients,

In terms of change from baseline in CGI-S score (the secondary outcome), both doses of risperidone ER (90 mg and 120 mg) and placebo group demonstrated an improvement at the end of the study (LSM: -0.87 [SE: 0.07], -0.91 [SE: 0.07], and -0.52 [SE: 0.07] in the risperidone ER 90 mg, risperidone ER 120 mg, and placebo groups, respectively). Compared with placebo, both risperidone ER 90 mg and risperidone ER 120 mg demonstrated a statistically significant improvement (risperidone ER minus placebo, LSMD, -0.35, 95% CI, -0.56 to -0.14, $P = 0.0002$ for risperidone ER 90 mg and LSMD, -0.40, 95% CI, -0.60 to -0.19, $P < 0.0001$ for risperidone ER 120 mg). For the CGI-S, neither the change from baseline for either risperidone ER treatment groups, nor the treatment group difference between risperidone ER group and placebo met the minimal important difference (i.e., a reduction of CGI-S of 1 point). Therefore, the clinical significance of the observed findings in CGI-S are unclear.

Health-related quality of life was assessed using the EQ-5D-5L. Patients' subjective well-being was estimated with the Subjective Well-being under Neuroleptic Treatment-Short Version (SWN-S) and patients' satisfaction with medication was examined with the Medication Satisfaction Questionnaire (MSQ). The results of the EQ-5D-5L, SWN-S, and MSQ were not presented in the sponsor's summary of the clinical evidence provided for this CADTH review.

Harms Results

The proportion of the patients who experienced at least 1 treatment emergent adverse event were reportedly higher for the risperidone ER 120 mg group (77.8%) compared with the risperidone ER 90 mg (70.4%) and placebo groups (68.6%). Overall, the most frequently reported treatment emergent adverse events occurring at higher rates in the risperidone ER groups compared with the placebo group were weight gain (13%, 12.8% and 3.4% in risperidone ER 90 mg, 120 mg, and placebo group, respectively) and somnolence (5.2%, 4.3%, and 0% in risperidone ER 90 mg, 120 mg, and placebo group, respectively).

There were no deaths reported during the treatment periods. The incidence of serious treatment emergent adverse events was infrequent (0%, 0.9%, and 0.8% in risperidone ER 90 mg, 120 mg, and placebo group, respectively). The proportion of patients who withdrew due to adverse events was reportedly low (0%, 1.7%, and 2.5%, in the risperidone ER 90 mg, 120 mg, and placebo group, respectively). Regarding the adverse events of special interest for this review, more patients (13%) in the risperidone ER groups experienced weight gain compared with patients with placebo (3.4%), which was an expected adverse event as reported in all other atypical antipsychotic drugs.

- Treatment with risperidone ER (90 mg and 120 mg) over an 8-week treatment period was generally well tolerated in adult patients with acute schizophrenia. There were no new safety signals compared with the known safety profile of oral LAI risperidone products.

Critical Appraisal

Overall design of the included study (Study 09-0010) was appropriate with respect to randomization, blinding, allocation concealment, and standardized assessment of the primary outcomes. Based on the information available in the sponsor's summary of the clinical evidence, the baseline demographic characteristics were generally well balanced across treatment arms in the pivotal study.

The proportion of patients who discontinued from the trials was relatively high (i.e., 22.4% to 29.4% across the treatment groups) for an 8-week study. Although the discontinuation rates were similarly high between the groups and not differential, this could potentially lead to an imbalance in baseline characteristics as the trial progressed and efficacy data at 8 weeks was

not available for a large number of patients. It is uncertain how the missing data could have impacted the study results. The mixed model for repeated measures analysis used assumes the data are missing at random (MAR), which is often not the case in clinical trials. Although a pattern sensitivity analysis suggests the MAR assumption was not violated, and supported the primary efficacy analysis, this approach also makes several assumptions to estimate the factors in the dropout pattern which are unclear. Moreover, although a multiple imputation approach was also used, this is only valid if the data missing from the dropouts were truly MAR. As a result, it is unclear what impact missing data may have had on the efficacy results observed.

The study was conducted in a distinct study population: patients were adults younger than 55 years, and the majority of patients were male and black, with a PANSS total score between 80 and 120, which may not fully represent the characteristics of Canadian patients with schizophrenia.

The 8-week duration of the double-blind randomized controlled trial phase was considered short to assess the long-term maintenance effect of treatment. However, the clinical expert consulted by CADTH for this review considered 8 weeks to be an adequate duration used in clinical trials for schizophrenia acute exacerbation to demonstrate a treatment effect. Nevertheless, the CADTH clinical expert indicated that while further studies are needed to assess the long-term efficacy (e.g., relapse, remission, hospitalization) and safety of risperidone ER, other formulation of risperidone (oral and LAI agents) have been available and used in Canadian clinical practice for a long time; therefore, a physician would likely have minimal concerns regarding the long-term efficacy and safety of risperidone ER.

Study 09-0010 was placebo-controlled. There was no direct or indirect treatment comparison evidence included in the sponsor's submission that compared risperidone ER with oral risperidone, risperidone LAI (IM biweekly) and other relevant existing AAP LAI marketed in Canada. The sponsor indicated that the efficacy of risperidone ER was similar to that observed for oral risperidone and risperidone LAI. According to the expert consulted by CADTH for this review, it is generally accepted that all LAIs are of similar efficacy, and lack of comparative data would be unlikely to influence prescribing of risperidone ER since the efficacy and safety profile of oral risperidone and risperidone LAIs has been well established, although the novel technology may make some clinicians cautious.

Economic Evidence

Cost and Cost-Effectiveness

The sponsor submitted a cost comparison evaluating the annual cost of risperidone extended release (ER) to risperidone long-acting injectable (LAI), risperidone tablets, aripiprazole LAI, and paliperidone LAI products. No evidence was submitted to support the sponsor's assumption of clinical similarity among LAI AAP comparators, and no evidence was submitted to support implicit assumptions of dose equivalency between LAI AAPs. Therefore, any conclusions regarding incremental costs or savings associated with the use of risperidone ER are uncertain.

At the submitted prices of \$456.18 (90 mg dose) and \$608.22 (120 mg dose), the annual cost of risperidone ER is \$5,474 to \$7,299 per patient. This annual cost is more expensive than that of risperidone tablets (\$349 to \$524 per patient annually) but within the range of other LAI AAPs (\$3,815 to \$8,877 per patient annually). A small amount of savings in drug administration may also be seen when risperidone ER is compared to risperidone LAI, due to its less frequent monthly versus biweekly dosing. However, the highest available dose of each LAI AAP comparator is the most frequently used. In order for the cost of the highest recommended dose of risperidone ER to equal that of the least expensive comparator at its highest recommended dose (aripiprazole LAI), the price of risperidone ER 120 mg would need to be reduced by 25%. These incremental costs (or savings) are based on publicly available list prices and may not reflect actual prices paid by Canadian public drug plans.

Budget Impact

CADTH's reanalysis of the sponsor's budget impact analysis included: removing the double counting of dispensing fees and markups and increasing the proportion of included patients assumed to be covered by public drug plans. Based on CADTH reanalysis, the budgetary impact of reimbursing risperidone ER for patients with schizophrenia is expected to be \$1,171 in year 1, \$32,179 in year 2, and savings of \$331,555 in year 3, for a 3-year cumulative budgetary savings of \$298,205. Given uncertainty in dose equivalency and the proportion of patients who will use each dose of risperidone ER, a scenario analysis was conducted reducing the proportion of patients using the lower risperidone ER dose; this scenario led to increased costs.

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Meeting date: July 21, 2021

Regrets: None

Conflicts of interest: None