CADTH

CADTH Drug Reimbursement Review

Pharmacoeconomic Report

NINTEDANIB (OFEV)

Boehringer Ingelheim Canada Ltd.

Indication: Chronic Fibrosing Interstitial Lung Diseases

Service Line:	CADTH Common Drug Review
Version:	Final (with redactions)
Publication Date:	April 2021
Report Length:	34 Pages

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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

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Abbreviations

AIC	Akaike information criterion
BIC	Bayesian information criterion
BSC	best supportive care
FVC	forced vital capacity
FVCPP	forced vital capacity percent predicted
ICER	incremental cost-effectiveness ratio
ILD	interstitial lung disease
IPF	idiopathic pulmonary fibrosis
LY	life-year
NIN	nintedanib
PF-ILD	progressive fibrosing interstitial lung disease
QALY	quality-adjusted life-year
UIP	usual interstitial pneumonia

Executive Summary

The executive summary comprises 2 tables (Table 1: Background and Table 2: Economic Evaluation) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Nintedanib (Ofev), 100 mg and 150 mg capsules
Submitted price	Nintedanib, 100 mg, oral soft capsule: $28.42 per capsule Nintedanib, 150 mg, oral soft capsule: $56.83 per capsule
Indication	Indicated for the treatment of chronic fibrosing ILDs with a progressive phenotype
Health Canada approval status	NOC
Health Canada review pathway	Priority review
NOC date	May 20, 2020
Reimbursement request	As per indication
Sponsor	Boehringer Ingelheim Canada Ltd.
Submission history	Previously reviewed: Yes Indication: For the treatment of idiopathic pulmonary fibrosis Recommendation date: October 15, 2015 Recommendation: Reimburse with clinical criteria and/or conditions

ILD = interstitial lung disease; NOC = Notice of Compliance.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov microsimulation model
Target population	Patients with chronic fibrosing ILD with a progressive phenotype
Treatment	Nintedanib plus BSC
Comparator	BSC (consisting of immunosuppressants)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (25 years)
Key data source	INBUILD trial
Submitted results for base case and key scenario analyses	ICER = $122,391 per QALY (incremental costs = $133,277, incremental QALYs = 1.089) Key subgroup analyses: • Patients presenting with UIP pattern: ICER = $123,464 per QALY • Patients presenting with non-UIP: ICER = $166,547 per QALY
Key limitations	• INBUILD trial outcome data were used to fit parametric extrapolations of overall survival separately for the comparator, BSC, and for NIN plus BSC. The approach assumed a substantial survival benefit for NIN plus BSC, although the trial was not powered to demonstrate a statistically significant reduction in mortality over 52 weeks. • To model the probability of remaining on NIN while alive, an exponential distribution was used for the extrapolation of data for time to discontinuation with NIN from the INBUILD trial. However, the clinical experts consulted by CADTH for this review noted that this distribution underestimated the likelihood of remaining on treatment. • Disease progression was modelled according to reduction in FVCPP. Different combinations of covariates within NIN plus BSC and BSC prediction models were included to estimate FVCPP over a patient's lifetime. The sponsor's selected prediction models likely resulted in an overestimation of total expected QALYs for NIN plus BSC. The clinical experts suggested that the model covariates should be identical, regardless of treatment assignment and that the covariates within the NIN plus BSC prediction model would be adequate to use as covariates in the BSC prediction model to estimate decreases in FVCPP. • Arbitrary FVCPP-based cut-offs were assigned to define disease progression (i.e., 10% decline in FVCPP from baseline) and immediate death (absolute FVCPP ≤ 40%). The appropriateness of the use of such criteria remains unclear as the validity of FVCPP in patients with progressive ILD has not been reported in the literature.
CADTH reanalysis results	• CADTH undertook reanalyses to address limitations relating to the extrapolations of overall survival and the time to the discontinuation of NIN to reflect more clinically plausible distributions and selected an alternate prediction model to estimate the change in FVCPP for BSC. • ICER: $154,688 per additional QALY gained ($142,585 incremental costs, 0.92 incremental QALYs). • CADTH noted that the results warrant careful interpretation since more than 99% of NIN plus BSC's incremental benefit was accrued in time points beyond which clinical data are available. • A price reduction of 77% was required for NIN plus BSC to achieve an ICER below $50,000 per QALY gained.

BSC = best supportive care; FVCPP = forced vital capacity percent predicted; ICER = incremental cost-effectiveness ratio; ILD = interstitial lung disease; LY = life-year; NIN = nintedanib; QALY= quality-adjusted life-year; UIP = usual interstitial pneumonia.

Conclusions

The INBUILD study reported that, in adult patients with progressive fibrosing interstitial lung disease (PF-ILD), the difference in mortality between nintedanib (NIN) plus best supportive care (BSC) compared with BSC alone was not statistically significant over 52 weeks. However, the assumed and extrapolated difference in mortality is a key driver in the economic analysis.

CADTH undertook reanalyses to address limitations relating to the following: the extrapolations of overall survival by selecting a gamma function which estimated more clinically plausible net survival benefits; modified the extrapolation of time to the discontinuation of NIN to a log-normal function to reflect what clinical experts considered to be more clinically plausible based on their existing experience with this drug; and, selected an alternate prediction model for change in forced vital capacity percent predicted (FVCPP) for BSC based on one that applied the same covariates as those used for the NIN plus BSC prediction model. Based on CADTH reanalysis, the incremental cost-effectiveness ratio (ICER) for NIN plus BSC compared with BSC was $154,688 per quality-adjusted life-year (QALY) gained, which aligned with the sponsor's findings. The probability that NIN plus BSC was cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained was 8%. A reduction of 77% in the price of NIN was required to improve its cost-effectiveness, relative to BSC, and generate an ICER less than $50,000 per QALY. While the survival benefit of NIN plus BSC relative to BSC alone, as estimated in the CADTH reanalysis (i.e., 1.38 additional life-years), was considered reasonable by the clinical experts consulted by CADTH, it is important to note that the INBUILD study was unable to demonstrate a statistically significant difference in mortality. In a scenario analysis where no survival benefit for NIN was assumed, the ICER for NIN plus BSC versus BSC increased to $317,832 per QALY gained. To address, in part, the heterogeneity of PF-ILD, subgroup analyses were further conducted for the usual interstitial pneumonia (UIP)-like and non-UIP fibrotic patterns. The ICER for NIN plus BSC for the UIP-like fibrotic pattern subgroup was $135,208 per QALY gained while the ICER for the non-UIP pattern subgroup was $185,321 per QALY gained when compared with BSC.

The results of CADTH's reanalyses remain uncertain as the model is sensitive to the survival benefit modelled and the regression model used to predict decreases in FVCPP over time. Both inputs represent substantial sources of uncertainty in the model and CADTH was unable to validate these aspects in the absence of long-term clinical efficacy data for NIN. Furthermore, given a lack of studies reporting the measurement properties of FVCPP in patients with PF-ILD, CADTH was unable to incorporate an evidence-based FVCPP cut-off to define disease progression.

Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups that participated in the CADTH review process.

Four patient groups (the Canadian Pulmonary Fibrosis Foundation, the Ontario Lung Association [newly named Lung Health Foundation], the British Columbia Lung Association, and Scleroderma Canada) participated in either an online survey, phone interview, and/or focus groups to contribute to CADTH's appraisal of the sponsor's pharmacoeconomic analysis of NIN for the treatment of patients with other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype.

PF-ILD is described as a fatal disease with symptoms and disease progression that vary between individuals. Symptoms of PF-ILD noted include breathing difficulties (shortness of breath or dyspnea), chronic cough, fatigue, low energy, muscle weakness, difficulty sleeping, and psychological complications (e.g., fear of isolation, inability to maintain focus or attention, general fear, anger, embarrassment, or depression). The development of such outcomes may reduce patients' quality of life. Immunosuppressants are often the standard of care in early disease management for PF-ILD. The patients expressed desire for the elimination or deceleration of disease progression; reductions in fatigue, cough, and shortness of breath; an improvement in energy; as well as reductions in caregiver burden and dependency on others for transportation as the overarching goals of treatment. Twelve patients who were treated with NIN reported some improvement in their disease symptoms, particularly shortness of breath and fatigue, but also reported various side effects, most notably gastrointestinal discomfort and intense diarrhea.

- The intervention and comparator (i.e., NIN plus BSC and BSC, respectively) were assumed to include the current standard of care for PF-ILD: immunosuppressant therapy.
- Utility decrements associated with some of the symptoms identified as related to treatment with NIN (i.e., diarrhea, vomiting, nausea) were accounted for.
- The option to estimate the societal impacts of NIN plus BSC versus BSC was included as a scenario analysis. The societal costs captured within the sponsor's model included the costs of informal care, transportation for hospitalization and health care visits, and patient's productivity loss with event rates based on a post hoc analysis of the INPULSIS trial.[1]

While the sponsor accounted for some quality of life impacts related to the condition and treatment with NIN, the sponsor did not explore other relevant considerations identified by the patient input in their economic analysis[2] As noted in the patient input, PF-ILD is associated with a myriad of symptoms that impact quality of life. The utility regression selected in the model only considered FVCPP, progression status, and current acute ILD exacerbation. It is not clear how these predictors within the utility regression relate to the PF-ILD symptoms that were cited in the patient input that impacted patients' quality of life (e.g., fatigue, low energy, muscle weakness, difficulty sleeping, and psychological complications).

Economic Review

The current review is for NIN (Ofev) for the treatment of patients with chronic fibrosing ILDs with a progressive phenotype.

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

The sponsor submitted a cost-utility analysis of NIN plus BSC versus BSC alone for the treatment of patients with chronic fibrosing ILD with a progressive phenotype.[2] BSC was assumed to consist of immunosuppressant therapy. The population was consistent with the Health Canada indication and the reimbursement request.

The recommended dose of NIN is 150 mg twice daily administered approximately 12 hours apart.[3] The management of adverse reactions associated with the use of NIN could include a dose reduction to 100 mg twice daily (i.e., titrated dose of 200 mg daily) or a temporary interruption of treatment until the specific adverse reaction has resolved to levels that allow for the continuation of therapy.[3] At the sponsor's submitted prices of $28.42 per 100 mg capsule and $56.83 per 150 mg capsule, the annual costs are $20,758 and $41,517 per patient for the respective drug strengths and dosages.[2] In the model, [redacted]% of patients were assumed to be treated with the 150 mg strength and [redacted]% with the 100 mg strength.[2] No drug acquisition cost was modelled for BSC as this was assumed to apply equally to both groups.

The clinical outcomes of interest were QALYs and life-years. The economic analysis was undertaken over a lifetime time horizon (25 years) from the perspective of the public health care payer. Discounting (1.5% per annum) was applied to both costs and outcomes.

Model Structure

The sponsor submitted a microsimulation model with the cycle length defined as 1 month.[2] The model first generated patients with unique health profiles using the distribution of baseline characteristics observed within the INBUILD trial. Each patient entered the model 1 at a time and, following treatment with either NIN plus BSC or BSC, had their disease trajectories separately tracked over their lifetime. Both the patient's characteristics and their history of prior events could influence their FVCPP level. FVCPP was assumed to worsen progressively (i.e., only decrease in value was possible) and was re-calculated at the end of each model cycle. Once an absolute decline of 10% or greater in FVCPP compared with baseline occurred, the patient was assumed to have progressed, resulting in a permanent utility decrement. When FVCPP decreased to 40% or less, the patient was assumed to have died. In addition, for patients on NIN plus BSC, the model re-assessed at the end of each cycle whether they would remain on NIN plus BSC or discontinue NIN and exclusively receive BSC. All patients who remained alive could experience an acute exacerbation that was dependent on their original treatment assignment. An acute exacerbation was defined according to the INBUILD trial based on meeting 3 criteria: acute worsening or development of dyspnea for 1 month or less; a computed tomography with new bilateral ground glass opacity and or consolidation superimposed on a background pattern consistent with fibrosing ILD; and deterioration not fully explained by cardiac failure or fluid overload. Within the model, a patient could experience only 1 acute exacerbation, and depending on their

initial treatment assignment, this resulted in different reductions in FVCPP (NIN plus BSC = –4.03%; BSC = –6.95%). Patients could transition at any time to the death health state, with the risk of death being treatment dependent (Appendix 3: Figure 1).

Model Inputs

The model's population and clinical parameters were primarily characterized according to the INBUILD study, which was a double-blind, randomized controlled trial evaluating the efficacy and safety of 150 mg of NIN twice daily over 52 weeks compared with placebo.[4] The sponsor assumed the INBUILD population (baseline characteristics: mean age = 66 years; FVCPP = 69%; male = 53.7%; 62% with UIP pattern; 31% with marginal decline in FVCPP [≥ 5% to < 10%] in 24 months before screening)[4] adequately reflected the Health Canada indication.

INBUILD trial outcome data, collected over 52 weeks based on the intention-to-treat population for each treatment arm, were used in separate linear regression analyses to fit prediction models that simulated decreasing FVCPP for each comparator over time. Both regression models included baseline age, current age, baseline FVCPP, and acute exacerbation as covariates; the model for BSC additionally included baseline outcomes of marginal (≥ 5% to < 10%) and clinically significant declines in FVCPP (≥ 10%), as well as the existing active exacerbation status and the current duration of marginal or clinically significant decline in FVCPP since baseline.[2] Furthermore, survival analyses of INBUILD trial's 52-week data censored for mortality and, if applicable, treatment discontinuation, and were conducted to inform 3 transition probabilities within the model: first acute exacerbation (see Figure 3, exponential function for both comparators); discontinuation of NIN (see Figure 4, exponential function); and mortality (see Figure 2, log-logistic function for both comparators). The curves were independently fitted for each treatment group with the parametric functions chosen according to goodness of fit statistics (Akaike information criterion [AIC] and Bayesian information criterion [BIC]) and visual fit.[2] Upon discontinuation of NIN, patients' mortality would continue to be modelled according to the extrapolated overall survival curve for NIN but disease progression, as measured by the reduction in FVCPP (and indirectly, mortality due to FVCPP ≤ 40%), was modelled according to the BSC prediction model.

Treatment-related adverse events were modelled if they had an incidence of greater than 10% in either treatment arms of the INBUILD trial and occurred at least 1.5 times more often in the NIN arm compared with placebo. As such, the sponsor only incorporated the incidence of diarrhea, vomiting, and nausea into their economic model.

Patient-specific utility values were calculated at each model cycle according to a linear mixed-effect regression model fitted based upon EuroQol 5-Dimensions 5-Levels questionnaire data collected in the INBUILD trial with UK-based tariffs applied.[4] The regression model was fit to assess utility as a function of the following patient characteristics as covariates: baseline utility value (0.704), baseline characteristics (age, UIP pattern, time since trial's initial diagnosis, marginal decline in FVCPP [≥ 5% to < 10%], clinically significant decline in FVCPP [≥ 10%]), and time-varying characteristics (FVCPP, acute exacerbation, and disease progression status). The utility decrement associated with an acute exacerbation that this regression model estimated (0.18) was only applied during the cycle in which the exacerbation occurred. Separate from the utility regression, each of the treatment-related adverse events were assumed to yield a temporary utility decrement of –0.034.[2]

The model included costs for drug acquisition, treatment-related adverse events and monitoring, follow-up care, acute exacerbation, and palliative care. Drug costs for NIN plus BSC were based on the sponsor's submitted prices.[2] Adverse events were assumed to incur the cost of an ambulatory care visit as outlined within the Ontario Case Costing Initiative.[5] As per NIN's product monograph,[3] a liver panel blood test was modelled every 3 months for patients taking NIN plus BSC based on the Ontario Schedule of Benefits for Laboratory Services.[6] Follow-up care comprised hospitalizations, emergency room visits, and outpatient visits to various health care providers (including a general practitioner, specialist, nurse, physiotherapist, occupational therapist, and other specialists). The costs for these resources were obtained from the Ontario Schedule of Benefits, Canadian Institute for Health information, the Job Bank of Canada, and other published sources.[5-7] The sponsor further incorporated INBUILD trial data to determine the monthly probability and frequency of using each of these resources according to the patients' current FVCPP category (i.e., 40 to 49.9, 50 to 59.9, 60 to 69.9, 70 to 79.9, 80 to 89.9, 90 to 99.9, ≥ 100).[4] The cost of an acute exacerbation were based on outcome data from the INPULSIS study.[1,8] Finally, palliative care costs were included according to published studies.[8-10]

Summary of Sponsor's Economic Evaluation Results

All analyses were run probabilistically (1,000 iterations, each with 500 simulated patients, for the base-case and scenario analyses). The deterministic and probabilistic results were similar. The probabilistic findings are presented below.

Base-Case Results

NIN plus BSC was associated with an incremental cost of $133,277 and 1.09 additional QALYs compared with BSC over a 25-year time horizon (Table 3). This resulted in an ICER of $122,391 per QALY gained for NIN plus BSC compared with BSC. Life-year outcomes and detailed results are presented in Table 11. The results were primarily driven by drug acquisition costs (see Table 11 for disaggregated results). NIN plus BSC was associated with 0.01 more QALYs than BSC during the trial period and 1.08 more QALYs in the extrapolated period. In other words, the majority of the QALY gains estimated (99.5%) occurred during the extrapolated period outside of the INBUILD trial period. In the sponsor's base case, NIN plus BSC had an 8% probability of being cost-effective at a willingness-to-pay threshold of $50,000 per QALY.

Table 3: Summary of the Sponsor's Economic Evaluation Results

Drug	Total costs ($)	Incremental costs ($)	Total QALYs	Incremental QALYs	ICER vs. BSC ($/QALY)
BSC	46,552		1.95		
NIN plus BSC	179,829	$133,277	3.04	1.09	122,391

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; NIN = nintedanib; QALY = quality-adjusted life-year; vs. = versus.

Note: The submitted analysis is based on the publicly available prices of the comparator treatments.

Source: Sponsor's pharmacoeconomic submission.[2]

Sensitivity and Scenario Analysis Results

The sponsor assessed several model parameters in probabilistic scenario analyses, as reported in Table 12. Four of these resulted in a greater than 10% increase in the ICER. Such notable increases occurred when alternative parametric functions were used to extrapolate overall survival for NIN plus BSC (Weibull) and for BSC (log-logistic; $138,112 per QALY gained). Further, in subgroup analyses of patients presenting with UIP-like fibrotic

patterns and in those with non-UIP patterns, the ICERs for NIN plus BSC compared with BSC were $123,464 and $166,547 per QALY gained, respectively.

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the economic analysis:

- **Inappropriate survival benefit modelled for NIN plus BSC compared with BSC:** Although the INBUILD trial was not powered to demonstrate a statistically significant reduction in mortality over 52 weeks, these data were used to fit parametric extrapolations of overall survival for NIN plus BSC and BSC. The sponsor's selected statistical distribution for overall survival (i.e., log-logistic) was partly justified based on visual fit to historical data from a study that evaluated mortality in patients with idiopathic pulmonary fibrosis (IPF) which is a different indication than the one currently under review.[11] The sponsor's chosen distribution led to substantial survival benefit assumed for NIN plus BSC compared with BSC (i.e., NIN plus BSC = 8.42 years versus BSC= 3.75 years) and, therefore, the total expected survival and QALYs for NIN plus BSC was likely inflated. According to CADTH's Clinical Review report, the Kaplan-Meier curve on the time to mortality over 52 weeks from INBUILD did not indicate a survival benefit for NIN relative to placebo, and accordingly, the estimated hazard ratio of mortality (HR = 0.94; 95% confidence interval, 0.47 to 1.86; P = 0.854) was not statistically significant.[12] The Clinical Review further suggested that this result was largely consistent across the UIP-like and non-UIP subgroups. Given the lack of overall survival data beyond the trial period for patients with chronic fibrosing ILD with a progressive phenotype, there is long-term uncertainty to the expected survival benefits of NIN. The clinical experts consulted by CADTH for this review expected a smaller difference in overall survival between the modelled treatment and its comparators. The gamma functions were identified to be more appropriate for both comparators.
    - CADTH revised the extrapolations of overall survival to gamma functions, based on the clinical experts' input. CADTH further explored the impacts of assuming no survival benefit for NIN plus BSC compared with BSC in a scenario analysis in light of the short-term findings arising from the available comparative clinical literature.
- **Uncertainty in the extrapolation of time to NIN discontinuation:** To estimate the probability that a patient who initiated NIN plus BSC would continue receiving NIN each month, rather than switch over to BSC, the sponsor selected an exponential function to extrapolate data on the time to treatment discontinuation. According to the sponsor, this was based on their interpretation of the functions' AIC and BIC statistics. AIC and BIC are statistical measures that indicate the degree to which a statistical model accurately predicts the observed data. The lower the AIC and BIC values, the better the fit of the model. The exponential function was chosen for its simplicity (single-parameter distribution) and its consistency with the extrapolation for acute exacerbations although, according to the reported AIC and BIC measures, this function provided the worst fit of all the parametric functions assessed (i.e., the highest AIC and BIC values). Based on the exponential function, the probability of remaining on NIN, conditional on being alive, at 5 years after treatment initiation was estimated to be 0.30. However, the clinical experts consulted by CADTH for this review suggested that this projection was an underestimate and that patients who remain alive are likely to have a more than 50% chance of remaining on NIN at year 5. As such, the experts expressed preference for incorporating a log-normal function to extrapolate data on the time to the discontinuation of NIN as this had improved face validity. Furthermore, according to the sponsor's reported AIC and BIC statistics, this parametric function was amongst the few distributions with the lowest values.
    - CADTH used a log-normal function to extrapolate the time to discontinuing NIN, based on the feedback from clinical experts.

- **Inappropriate use of alternative prediction models for estimating decreases in FVCPP between comparators:** To model disease progression, lung function decline was defined by a reduction in FVCPP. This was estimated using linear mixed-effect regression analyses on the FVC outcomes reported in the 52-week INBUILD trial. Two approaches were considered: the application of 2 independent models (i.e., considers trial arms separately) versus 1 general model (i.e., considers the relative difference between the 2 arms). In the sponsor's base case, covariates for the independent models were selected using a backwards step-wise selection process with a P value cut-off of 0.05.[13] The FVCPP prediction model for BSC comprised 4 additional covariates than that incorporated in the NIN plus BSC prediction model, which were all related to marginal (≥ 5% to < 10%) or clinically significant declines in FVCPP. The inclusion of different combinations of covariates within the NIN plus BSC and BSC's prediction models raised concerns about the face validity of each model, particularly since patients in both the BSC arm and the NIN plus BSC arm have the same underlying disease. When presented with the covariates of each model, the clinical experts consulted by CADTH for this review did not find the additional covariates characterizing BSC's FVCPP model to be clinically necessary when compared with patients on NIN plus BSC. The experts further suggested that the covariates selected in the regression model for the NIN plus BSC comparator would be clinically relevant to predict decreases in FVCPP for patients irrespective of the current assigned treatment.
    - According to a request for additional information, the sponsor provided CADTH with a revised economic model in which the regression equation to predict patient FVCPP for BSC comprised the same set of covariates as that used for NIN plus BSC (i.e., baseline age, current age, baseline FVCPP, and ongoing acute exacerbation event). This regression for BSC was selected in the CADTH base case. As AIC and BIC statistics were not provided for any of the prediction models to properly evaluate model fit, CADTH conducted scenario analysis using alternative prediction models to evaluate the sensitivity of the economic analysis to the regression model selected (e.g., adoption of the general model).
- **Uncertainty in FVCPP-based cut-offs for modelling disease progression:** FVCPP was chosen, according to the INBUILD trial's outcome data, as the indicator for disease progression within the model. According to the CADTH Clinical Review, FVCPP is likely an appropriate end point, as it is well accepted by regulatory bodies such as the FDA and Health Canada, and the clinical experts consulted by CADTH for this review agreed.[12] However, within the model, the sponsor arbitrarily assumed that a cut-off for a clinically significant decline in FVCPP would be 10% from the baseline. Furthermore, a threshold of FVCPP of 40% or less corresponded to immediate death. The appropriateness of the use of such FVCPP-based criteria remains unclear as these outcomes for patients with progressive ILD have not been reported. According to the CADTH Clinical Review, current evidence of a minimum clinically important difference in FVCPP is limited to patients with IPF.
    - CADTH explored the use of a different cut-offs for disease progression in a scenario analysis based the range of the expected minimum clinically important difference identified for patients with IPF (i.e., decline in FVCPP was 5% since baseline).

Additionally, the following key assumptions were made by the sponsor and have been appraised by CADTH (see Table 4).

Table 4: Key Assumptions of the Submitted Economic Evaluation

Sponsor's key assumption	CADTH comment
The INBUILD trial population was used to define the model population on the basis that the trial study adequately represented the indication for this review.	Reasonable. As noted by the clinical experts in the CADTH Clinical Review, the population in INBUILD likely reflected populations that they would expect to treat with this condition. Minor exceptions to this stance are highlighted in the Issues for Consideration section.
The clinical course of PF-ILD was exclusively modelled to be progressive in nature.	Likely appropriate based on feedback provided by the clinical experts, who did not expect overall prognosis (e.g., as defined by FVCPP) to improve over time.
Each patient could only experience a single acute exacerbation event over their lifetime. The available option to model multiple events did not account for changes in the probability of an event given the occurrence of prior events.	Potentially conservative given the rates of acute exacerbation was numerically higher in the comparator arm in the INBUILD trial. According to the clinical experts consulted by this review, the probability of experiencing a second or third acute exacerbation does not equal the probability of the first one (i.e., dependent probabilities). However, there is limited data to inform how these may be correlated. A scenario analysis was conducted by CADTH in which, similar to the sponsor sensitivity analyses, modelled the possibility of up to 3 independent acute exacerbation events (Table 12).
Only serious adverse events reported within the trial that had an incidence of > 10% in either treatment arms of the INBUILD trial and occurred at least 1.5 times more often in the NIN arm compared with placebo were included within the model.	Likely underestimates the utility decrement associated with NIN use. For example, the effects of altered liver enzyme levels, weight loss, difficulty with recall of information, and loss of smell and taste were not accounted for. Most importantly, drug-induced liver injury is a serious adverse event that is associated with NIN use that was not accounted for within the model. Health Canada issued a safety warning regarding drug induced liver injury in 2018[14] which is noted in NIN's product monograph.[3]
No treatment acquisition cost was modelled for BSC comparator.	Reasonable. Similar standard of care is required and it remains unclear to what extend immunosuppressant therapy can be reduced when on NIN. A simplifying assumption was therefore made by the sponsor that drug acquisition costs for BSC would be equal between the treatment and comparator arm and, therefore, would not need accounting for.
The probability of resource use and the frequency of use depended on the patient's current FVCPP category (i.e., 40 to 49.9, 50 to 59.9, 60 to 69.9, 70 to 79.9, 80 to 89.9, 90 to 99.9, and 100 to 109.9). Those with FVCPP ≥ 110 were assumed to have health care resource utilization similar to the FVCPP strata of 100 to 109.9.	The clinical experts consulted by CADTH for this review noted that the cost of resource use should increase as the FVCPP category decreased. Several of the modelled costs per category generally did not reflect this trend. For example, the cost assigned to characterize all follow-up care costs for the 80 to 89.9 group was less than that of the 90 to 99.9 group.
The cost of an acute exacerbation event was based on data collected in patients with IPF.	Potentially inappropriate as the actual cost of an acute exacerbation event in patients with PF-ILD remains unknown but unlikely to be a model driver.

BSC = best supportive care; FVCPP = forced vital capacity percent predicted; IPF = idiopathic pulmonary fibrosis; NIN = nintedanib; PF-ILD = progressive fibrosing interstitial lung disease.

CADTH Reanalyses of the Economic Evaluation

Base-Case Results

CADTH undertook reanalyses that addressed limitations within the model, as summarized in Table 5.

Table 5: CADTH Revisions to the Submitted Economic Evaluation

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections[a] to sponsor's base case		
None		
Changes to derive the CADTH base case		
1. Inappropriate survival benefit modelled for NIN plus BSC compared with BSC	Parametric function selected to extrapolate overall survival • NIN plus BSC = log-logistic • BSC = log-logistic	Parametric function selected to extrapolate overall survival • NIN plus BSC = gamma • BSC = gamma
2. Uncertainty in the extrapolation of time to NIN discontinuation	Exponential function selected to extrapolate time to discontinuing NIN	Log-normal function selected to extrapolate time to discontinuing NIN
3. Alternative prediction models used for estimating FVCPP over lifetime	Covariates in the FVCPP prediction model: • BSC ○ baseline age ○ current age ○ ongoing acute exacerbation event ○ marginal decline in FVCPP (≥ 5% to < 10%) in 24 months before screening at baseline ○ duration spent in marginal decline in FVCPP since baseline ○ clinically significant decline in FVCPP (≥ 10%) in 24 months before screening at baseline ○ duration spent in marginal decline in FVCPP since baseline	Covariates in the FVCPP prediction model: • BSC ○ baseline age ○ current age ○ baseline FVCPP ○ ongoing acute exacerbation event
CADTH base case	Combine revisions 1 + 2 + 3	

BSC = best supportive care; FVCPP = forced vital capacity percent predicted; NIN = nintedanib.

Note: The submitted analysis is based on the publicly available prices of the comparator treatments.

[a] Corrections are minor errors (e.g., transcription errors between report and model, misapplication of distributions, or standard errors in probabilistic analyses) that are not identified as limitations.

CADTH undertook a stepped analysis, incorporating each change proposed in Table 5 to sponsor's base case to highlight the impact of each change in Table 6.

Table 6: Summary of the Stepped Analysis of the CADTH Reanalysis Results

Stepped analysis	Drug[a]	Total costs ($)	Total QALYs	ICER ($/QALYs)
Sponsor's base case	BSC	46,552	1.95	122,391
	NIN plus BSC	179,829	3.04	
CADTH reanalysis 1	BSC	46,980	1.94	153,982
	NIN plus BSC	160,719	2.68	
CADTH reanalysis 2	BSC	47,231	1.96	133,118
	NIN plus BSC	215,834	3.23	
CADTH reanalysis 3	BSC	47,417	1.92	123,328
	NIN plus BSC	178,067	2.98	
CADTH base case (1 + 2 + 3)	BSC	47,550	1.93	154,688
	NIN plus BSC	190,135	2.85	

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; NIN = nintedanib; QALY = quality-adjusted life-year

Note: The reanalysis is based on the publicly available prices of the comparator treatments.

[a] Reference product is least costly alternative.

The stepped analyses were combined in the CADTH base case. The probabilistic results of CADTH's base case included publicly available prices of the comparator treatments and reflected the Health Canada-indicated population (Table 6). NIN plus BSC was $142,585 more costly and generated 0.92 additional QALYs than BSC. The ICER for NIN plus BSC versus BSC was $154,688 per additional QALY gained (disaggregated results are presented in Table 13). The likelihood that NIN plus BSC represented the most cost-effective strategy was 8% if the willingness-to-pay threshold was $50,000 per QALY.

The sponsor's model was not programmed to report total expected QALYs for the trial and extrapolated periods separately. Based on a deterministic analysis of CADTH's base case in which a 1-year time horizon was used and compared with the CADTH base case over a lifetime horizon, more than 99% of NIN plus BSC's incremental benefit compared to BSC was found to be accrued during the extrapolated period (Table 12).

Scenario Analysis Results

CADTH undertook price reduction analyses in the sponsor's base case and in CADTH's base case, assuming proportional price reductions for NIN (Table 7). A price reduction of 77% would be required for NIN plus BSC to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY.

Table 7: CADTH Price Reduction Analyses

	ICERs for NIN plus BSC versus BSC ($/QALY)	
Price reduction	**Sponsor base case**	**CADTH reanalysis**
No price reduction	122,391	154,688
10%	116,415	140,592
20%	105,681	127,127
30%	94,675	113,100
40%	83,988	99,432
50%	73,027	85,997
60%	62,054	72,168
70%	51,399	58,285
80%	40,647	44,772
90%	29,725	30,968

ICER = incremental cost-effectiveness ratio; NIN plus BSC = nintedanib plus best supportive care; QALY = quality-adjusted life-year.

Note: The submitted results were based on the publicly available prices of the comparator treatments.

CADTH also performed analyses on alternate scenarios (Table 14). The scenarios included an assumption of equal overall survival between NIN plus BSC and BSC, use of the sponsor's general model to predict decreases in FVCPP, the possibility of experiencing up to 3 acute exacerbations over a lifetime, use of 5% decline in FVCPP from baseline to define disease progression, assuming all patients receive NIN 100 mg twice a day, assuming all patients receive NIN 150 mg twice a day, and adoption of a societal perspective. Of these, CADTH's ICER most notably changed when the same overall survival extrapolation was applied to both treatment comparators ($317,832 per QALY gained), indicating significant uncertainty associated with the assumed survival benefit modelled for NIN within the CADTH base case. CADTH's ICER also changed when the general model was selected to predict decreases in FVCPP over time ($101,227 per QALY gained). This highlights the predictions of FVCPP to be a substantial source of uncertainty within the model.

CADTH conducted additional subgroup analyses on predefined subpopulations of the INBUILD trial: patients with UIP-like fibrotic patterns on high resolution computed tomography and those with other non-UIP fibrotic patterns (Table 14). The ICER for NIN plus BSC compared with BSC for the UIP-like fibrotic pattern subgroup was $135,208 per QALY gained and for the non-UIP pattern subgroup was $185,321 per QALY gained.

Issues for Consideration

- Nintedanib was previously reviewed by CADTH for the treatment of adult patients with IPF.[15] The CADTH Canadian Drug Expert Committee (CDEC) provided a conditional positive recommendation for NIN if clinical criteria and conditions were met. The clinical criteria were that forced vital capacity (FVC) needed to be greater than or equal to 50% of predicted and treatment with NIN should be discontinued if absolute FVC declines by 10% or greater within any 12-month period while receiving therapy. Additional conditions to the CDEC recommendation were that patients treated with NIN needed to be under the care of a specialist with experience in the diagnosis and management of IPF and the drug plan cost for NIN must not exceed the drug plan cost for pirfenidone. Publicly available prices for NIN are available (although the confidentially negotiated price remains unknown). For instance, within Ontario's Exceptional Access Program drug formulary, the public prices for NIN are aligned with the sponsor's submitted price for this review; $28.4168 per 100 mg capsule and $56.8336 per 150 mg.[16]
- Current treatments for PF-ILD include off-label immunosuppressants. The clinical experts consulted by CADTH for this review noted that depending on the specific diagnosis and the phase of the disease, a patient with PF-ILD may have entirely fibrotic disease or a combination of inflammation and fibrosis. As such, the experts noted a role for antifibrotics in the management of PF-ILD. Like NIN, pirfenidone is an antifibrotic which is approved for the management of IPF. This drug has been reviewed by CADTH for this indication in 2015.[17] The clinical experts reported that pirfenidone, typically prescribed as 801 mg 3 times daily, could be used off label to treat PF-ILD. However, in many jurisdictions, access to both this medication and NIN is currently significantly limited unless health care providers explicitly identify IPF in the diagnosis. Although there may be a potential role for pirfenidone in the management of PF-ILD, this has not been modelled as a treatment comparator within the current analysis and would not be possible given comparative data on the efficacy of pirfenidone relative to NIN is not available to facilitate its inclusion.
- The clinical experts consulted by CADTH noted that this indication is highly heterogeneous. Although attempts were made in the INBUILD trial to reflect the expected target population, patients with more severe disease, such as those with pulmonary hypertension, were excluded from the clinical trial. The clinical experts further noted that the specific inclusion criteria of 10% lung involvement on high resolution computed tomography within the INBUILD trial is unlikely to be an expectation for eligibility for NIN in clinical practice. This type of assessment takes a significant amount of time and skill and, unless quantified using machine learning, is subject to wide inter-rater variations. It is unclear how the INBUILD trial population would differ from the patients with PF-ILD in Canada who do not meet this inclusion criteria, and this uncertainty is further introduced into the economic analysis.
- The clinical experts consulted by CADTH expected that, in practice, the most common causes of discontinuation of NIN within this indication would be due to intolerable adverse effects. This aligns with the economic analysis in which treatment discontinuation was modelled according to data collected within the INBUILD trial in which discontinuation occurred predominantly due intolerable adverse events (65 out of 80 patients).

Overall Conclusions

In adult patients with PF-ILD, the use of NIN in addition to BSC was associated with a statistically significantly smaller decline in FVC at 52 weeks since baseline compared with BSC alone but no statistically significant difference in mortality was reported, as per the INBUILD study. However, the assumed and extrapolated difference in mortality is a key driver in the economic analysis.

CADTH identified limitations with the sponsor's analysis including: an implausible survival benefit modelled for NIN plus BSC compared with BSC; underestimation of time on NIN treatment; uncertainties in the prediction models used for estimating FVCPP over lifetime between treatments; and uncertainties to the appropriateness of FVCPP-based cut-offs to model disease progression. The CADTH reanalyses attempted to address some of the identified limitations with the sponsor's model by revising the extrapolations of overall survival for both comparators to gamma functions as well as for the time to discontinuation of NIN based on the clinical experts' input and incorporating an alternate prediction model to estimate patient FVCPP for the BSC that was based upon the same covariates as those used for the NIN plus BSC prediction model. In the CADTH base-case reanalysis, the ICER for NIN plus BSC compared with BSC was $154,688 per QALY gained, which aligned with the sponsor's findings. The probability that NIN plus BSC was cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained was 8%. Price reductions of at least 77% are required for NIN plus BSC to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained.

The majority (over 99%) of the incremental QALYs estimated for NIN plus BSC occurred during the extrapolated period and arose from the assumed survival benefit modelled for NIN. While the survival benefit of NIN plus BSC alone relative to BSC, as estimated in the CADTH reanalysis (i.e., 1.38 additional life-years), was considered reasonable by the clinical experts consulted by CADTH, it is important to note that the INBUILD study was unable to demonstrate a statistically significant difference in mortality. In a scenario analysis where no survival benefit for NIN was assumed, the ICER for NIN plus BSC versus BSC increased to $317,832 per QALY gained.

PF-ILD is a highly heterogeneous indication, as noted by the clinical experts consulted by CADTH. Subgroup analyses were conducted for the UIP-like fibrotic pattern and non-UIP pattern subgroups. The ICER for NIN plus BSC compared with BSC for the UIP-like fibrotic pattern subgroup was $135,208 per QALY gained and for the non-UIP pattern subgroup was $185,321 per QALY gained.

The results of CADTH's reanalysis remain uncertain as the model is sensitive to the survival benefit modelled for NIN and the regression model used to predict decreases in FVCPP over time. Both inputs represent substantial sources of uncertainty in the model and CADTH was unable to validate these aspects in the absence of long-term clinical efficacy data for NIN. Furthermore, given a lack of studies reporting the measurement properties of FVCPP-based data in patients with PF-ILD, CADTH was unable to incorporate an evidence-based FVCPP cut-off to define disease progression.

Appendix 1: Cost Comparison Table

The comparators presented in the following table have been deemed to be appropriate based on feedback from clinical experts. Comparators may be recommended (i.e., appropriate) practice or actual practice. Existing Product Listing Agreements are not reflected in the table and as such, the table may not represent the actual costs to public drug plans.

Table 8: CADTH Cost Comparison Table for Chronic Fibrosing Interstitial Lung Diseases With a Progressive Phenotype

Treatment	Strength	Form	Price ($)	Recommended dosage	Daily cost ($)	Annual cost[a] ($)
Nintedanib (Ofev)	100 mg 150 mg	Capsule	28.4168[b] 56.8336[b]	150 mg twice daily	113.67	41,517

[a] Annual cost calculated by assuming there are 365.25 days in a year.

[b] Sponsor submitted price.

Table 9: CADTH Cost Comparison Table for Treatments Used for the Treatment of Chronic Fibrosing Interstitial Lung Diseases With a Progressive Phenotype (Not Indicated)

Treatment	Strength	Form	Price ($)	Recommended dosage	Daily cost ($)	Annual cost[a] ($)
Antifibrotic						
Pirfenidone (Esbriet)	267 mg	Hard capsule	13.6251[b]	801 mg 3 times daily	120.82	44,128
	267 mg 801 mg	Film-coated tablets	13.4241[b] 40.2720[b]			
Immunosuppressants						
Azathioprine (Imuran, generics)	50 mg	Tablet	0.2405	1.5 mg/kg to 2.0 mg/kg daily	0.72 to 0.96	264 to 351
Cyclophosphamide (Procytox, generics)	25 mg 50 mg	Tablet	0.3520 0.4740	1.5 mg/kg to 2.0 mg/kg daily	1.30 to 1.42	475 to 519
	200 mg 500 mg 1,000 mg 2,000 mg	Vial	74.23[c] 91.31[c] 165.52[c] 304.46[c]	15 mg/kg monthly	239.75[d]	2,877[e]
Methotrexate (Metoject, generics)	2.5 mg 10 mg	Tablet	0.6325 2.7000[b]	15 mg to 20 mg weekly	3.97 to 5.40[f]	206 to 281
	20 mg/2 mL 50 mg/2 mL	Vial	12.5000 8.9200		12.50[f]	650
	7.5 mg 10 mg 12.5 mg 15 mg 17.5 mg 20 mg 22.5 mg 25 mg	Pre-filled syringe	28.0800[b] 29.6400 31.2000 32.7600 24.0000 26.2500 26.2500 29.2500		26.25 to 32.76[f]	1,365 to 1,704
Mycophenolate mofetil (CellCept, generics)	250 mg	Capsule	0.3712	1,000 mg to 1,500 mg twice daily	2.97 to 4.45	1,085 to 1,627
	500 mg	Tablet	0.7423			

Treatment	Strength	Form	Price ($)	Recommended dosage	Daily cost ($)	Annual cost[a] ($)
Mycophenolate sodium (Myfortic, generics)	180 mg 360 mg	Tablet	1.4983 2.9965	720 mg to 1,080 mg twice daily	11.99 to 17.98	4,378 to 6,567

Note: All prices are from the Ontario Drug Benefit formulary (accessed September 2020) unless otherwise indicated, and do not include dispensing fees.[7] All weight-based doses were based on an assumed weight of 76.94 kg, based on the average weight observed in the INBUILD trial.[4] All doses for off-label therapies were provided by clinical experts consulted by CADTH for this review.

[a] Annual cost calculated by assuming there are 365.25 days in a year and 52 weeks in a year.

[b] Saskatchewan Drug Plan Formulary (accessed October 2020).[18]

[c] Delta PA (accessed August 2020).[19]

[d] Cost provided is per month rather than per day.

[e] Twelve monthly doses assumed per year.

[f] Cost provided is per week rather than per day.

Appendix 2: Submission Quality

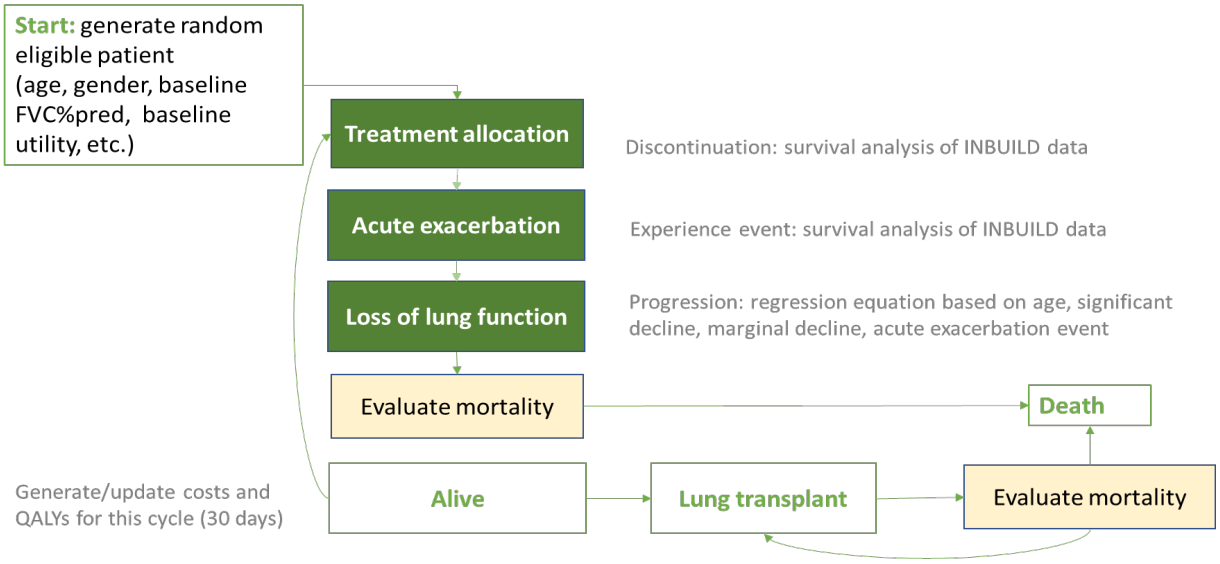
Table 10: Submission Quality

Description	Yes	No	Comments
Population is relevant, with no critical intervention missing, and no relevant outcome missing	☒	☐	The modelled comparator included 1 treatment that was relevant to the Canadian landscape, BSC. This comparator, like the drug under review, was assumed to include immunosuppressant therapy. However, other antifibrotics such as pirfenidone, which could potentially displace treatment with NIN in practice, were not included.
Model has been adequately programmed and has sufficient face validity	☒	☐	The model was adequately programmed, but disaggregated results of expected QALYs were not included and various aspects which were not key drivers of the model had limited face validity. For example, in scenario analyses in which more than 1 acute exacerbation could be modelled, the probability of experiencing a second or third acute exacerbation did not equal the probability of the first (i.e., dependent probabilities) according to the clinical experts consulted by CADTH but was modelled based on the assumption that the probabilities were all the same.
Model structure is adequate for decision problem	☒	☐	The model structure was adequate for the decision problem according to the clinical experts consulted. However, specific aspects of the chosen structure limited CADTH's ability to investigate the impact of varying assumptions (e.g., health care resource use structurally linked to FVCPP categories).
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis)	☒	☐	The model varied all parameters in the probabilistic analysis.
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem	☐	☒	Parameter uncertainty was adequately incorporated within the model. However, the model did not permit adequate explorations of structural uncertainty within the modelled regression equations.
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough details)	☐	☒	The report was generally well organized but had notable gaps in the information it presented about the model. For example, the report did not describe how patient characteristics (e.g., age, FVCPP at baseline) were sampled from distributions.

BSC = best supportive care; FVCPP = forced vital capacity percent predicted; QALY = quality-adjusted life-year.

Appendix 3: Additional Information on the Submitted Economic Evaluation

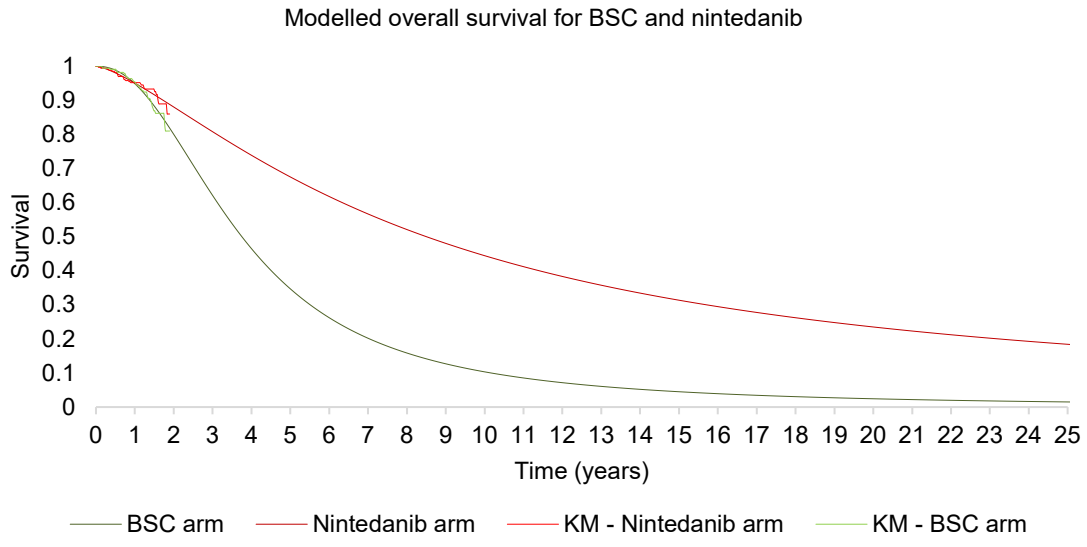
Figure 1: Model Structure



FVC%pred = FVCPP; QALY = quality-adjusted life-year.

Source: Sponsor's submission.[2]

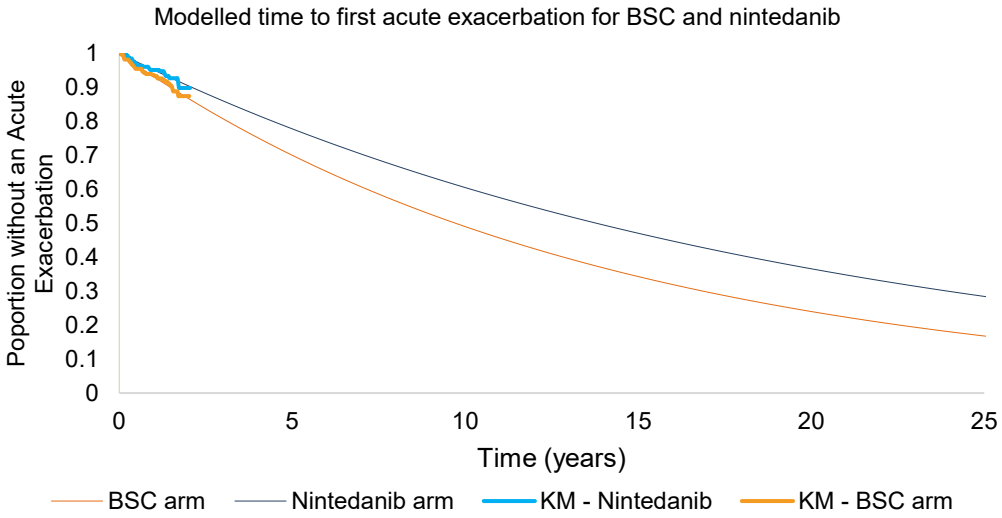
Figure 2: Kaplan-Meier Plots From the INBUILD Trial and Log-Logistic Extrapolations of Overall Survival for Each Treatment Comparator



BSC = best supportive care; KM = Kaplan-Meier.

Source: Sponsor's submission.[2]

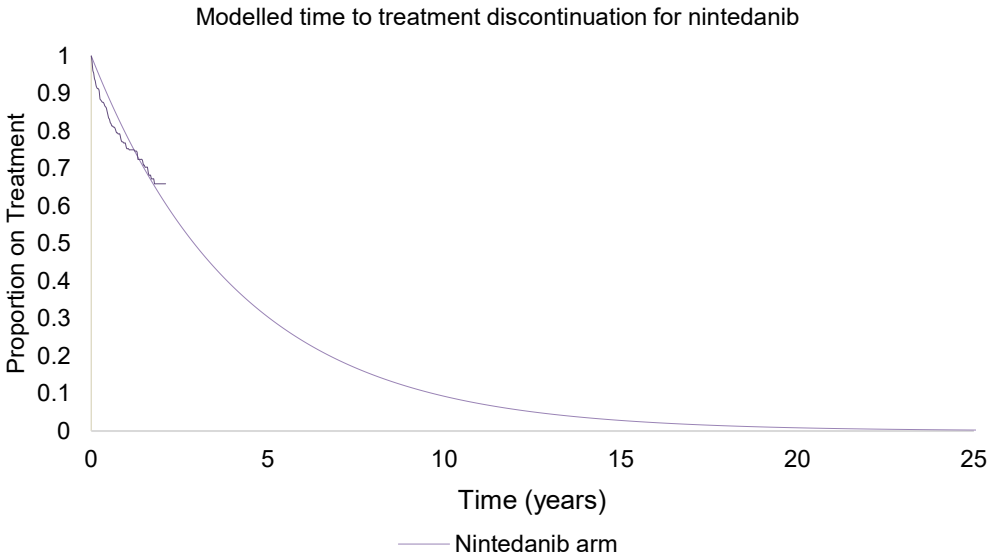
Figure 3: Kaplan-Meier Plots From the INBUILD Trial and Exponential Extrapolations Depicting Time to First Acute Exacerbation for Each Treatment Comparator



BSC = best supportive care; KM = Kaplan-Meier.

Source: Sponsor's submission.[2]

Figure 4: Kaplan-Meier Plot From the INBUILD Trial and Exponential Extrapolation Depicting Time to Treatment Discontinuation for the Nintedanib Plus BSC Comparator



Source: Sponsor's submission.[2]

Detailed Results of the Sponsor's Base Case

Table 11: Disaggregated Summary of the Sponsor's Economic Evaluation Results

Parameter	NIN plus BSC	BSC	Incremental	Percentage (of total incremental)[a]
Discounted LYs				
Total	4.71	3.05	1.66	100
Discounted QALYs				
Total	3.04	1.31	1.09	
Trial period	0.65	0.64	0.01	0.5
Extrapolation period	2.40	1.31	1.08	99.5
Discounted costs ($)				
Total	179,829	46,552	133,277	100
Treatment acquisition costs	112,818	0	112,818	84.6
Adverse events costs	1,700	345	1,355	1.0
Liver panel tests	702	0	702	0.5
Patient monitoring costs	50,412	32,052	18,360	13.8
Acute exacerbation costs	2,945	2,668	277	0.2
End of life costs	11,253	11,486	–234	–0.2
ICER ($/QALY)	122,391			

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life-year; NIN = nintedanib; QALY = quality-adjusted life-year.

Source: Sponsor's pharmacoeconomic submission.[2]

Table 12: Probabilistic Results of Sponsor's Scenario Analyses

Scenario		ICER ($/QALY)
Sponsor's base case		122,391
1	Weibull extrapolation of OS for BSC and log-logistic for NIN	107,635
2	Log-logistic extrapolation of OS for BSC and Weibull for NIN	138,112
3	Weibull extrapolation of OS for BSC and for NIN	117,907
4	FVCPP progression based on general regression model fit to dataset containing outcomes from both comparators of the INBUILD trial	69,215
5	Log-logistic extrapolation of time to first acute exacerbation for BSC and for NIN	122,719
6	Log-normal extrapolation of time to first acute exacerbation for BSC and for NIN	121,540
7	Weibull extrapolation of time to first acute exacerbation for BSC and for NIN	123,804
8	Log-logistic extrapolation of time to NIN discontinuation	128,659
9	Log-normal extrapolation of time to NIN discontinuation	128,734
10	Weibull extrapolation of time to NIN discontinuation	129,317
11	Excluded random effect from utilities model inclusion	121,525
12	Hospital cost per day = $1,485.11	119,743
13	Hospital cost per day = $1,400.23	119,000
14	Time horizon = 10 years	135,386
15	Time horizon = 5 years	195,776
16	Time horizon = 3 years	368,882

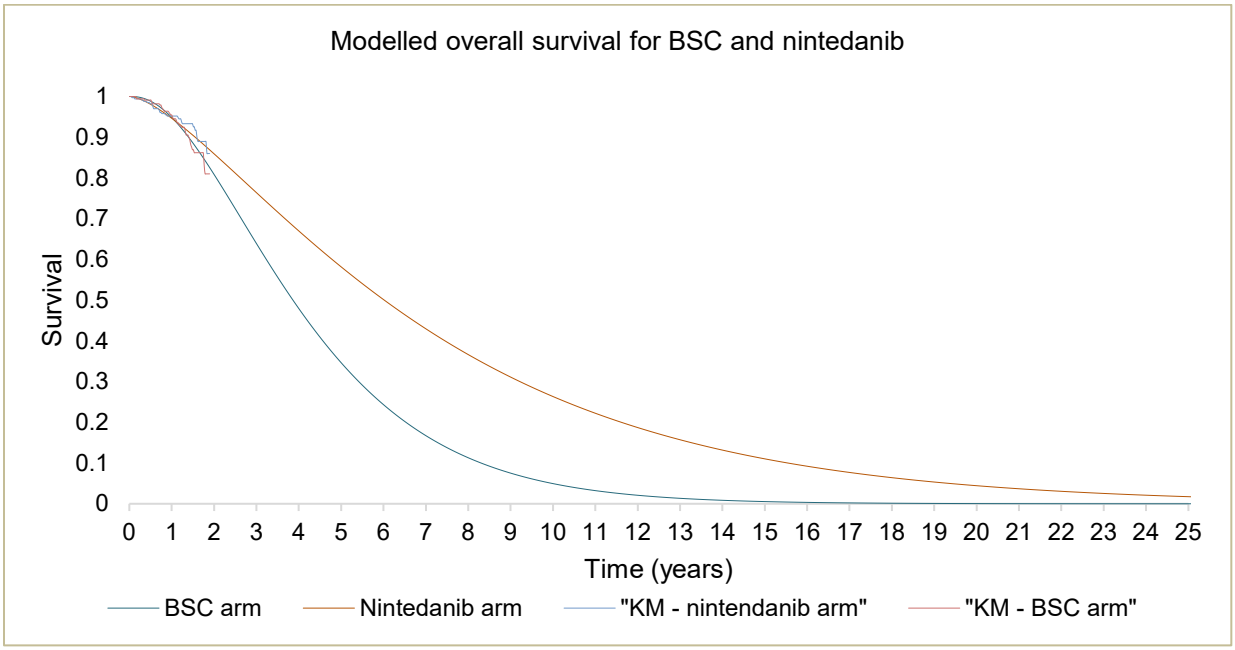
BSC = best supportive care; FVCPP = forced vital capacity percent predicted; ICER = incremental cost-effectiveness ratio; OS = overall survival; QALY = quality-adjusted life-year.

Source: Sponsor's pharmacoeconomic submission.[2]

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

Detailed Results of CADTH Base Case

Figure 5: Kaplan-Meier Plots From the INBUILD Trial and Gamma Extrapolations of Overall Survival for Each Treatment Comparator



BSC = best supportive care; KM = Kaplan-Meier.

Source: Sponsor's pharmacoeconomic submission.[2]

Table 13: Disaggregated Summary of CADTH's Economic Evaluation Results

Parameter	NIN plus BSC	BSC	Incremental	Percentage (of total incremental)[a]
Discounted LYs				
Total	4.44	3.06	1.38	100
Discounted QALYs				
Total	**2.85**	**1.93**	**0.92**	**100**
Trial period[b]	0.65	0.65	0.01	0.9
Extrapolation period[b]	2.20	1.29	0.91	99.1
Discounted costs ($)				
Total	**190,135**	**47,550**	**142,585**	**100**
Treatment acquisition costs	126,691	0	126,691	88.9
Adverse events costs	1,812	346	1,465	1.0
Liver panel tests	772	0	772	0.5
Patient monitoring costs	46,654	32,605	14,050	9.9

Parameter	NIN plus BSC	BSC	Incremental	Percentage (of total incremental)[a]
Acute exacerbation costs	2,861	3,112	–251	–0.2
End of life costs	11,346	11,488	–142	–0.1
ICER ($/QALY)	154,688			

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life-year; NIN = nintedanib; QALY = quality-adjusted life-year; vs. = versus.

[b] Disaggregated total expected QALYs reported for the trial and extrapolation periods are based on the deterministic results as the sponsor's model was not programmed to generate these outputs.

Scenario Analyses

Table 14: Probabilistic Results of CADTH's Scenario Analyses

Drug	Total costs ($)	Total QALYs	ICER ($/QALY)
Scenario 1: Overall survival was assumed to be equal between NIN plus BSC and BSC based on an extrapolation time to mortality data collected with the INBUILD trial's placebo comparator using a gamma function			
BSC	47,497	1.93	
NIN plus BSC	149,833	2.25	317,832
Scenario 2: The regression equation used to estimate FVCPP decreases over a patient's lifetime was based on the sponsor's general model (i.e., outcome data from both treatment arms within the INBUILD trial were pooled and analyzed using a single prediction model)			
BSC	46,018	1.87	
NIN plus BSC	197,968	3.37	101,227
Scenario 3: A patient could develop up to 3 acute exacerbations over a lifetime			
BSC	47,936	1.93	
NIN plus BSC	190,795	2.25	154,153
Scenario 4: Definition of disease progression was based on a decline in FVCPP of 5% since baseline			
BSC	47,555	1.89	
NIN plus BSC	190,239	2.79	157,803
Scenario 5: UIP-like subgroup			
BSC	45,381	1.84	
NIN plus BSC	180,842	2.85	135,208
Scenario 6: Non–UIP-like subgroup			
BSC	47,555	1.89	
NIN plus BSC	190,239	2.79	185,321
Scenario 7: All patients took the 100 mg capsule of NIN twice each day			
BSC	47,518	1.93	
NIN plus BSC	166,480	2.85	128,983
Scenario 8: All patients took the 150 mg capsule of NIN twice each day			
BSC	47,518	1.93	
NIN plus BSC	200,633	2.85	166,488
Scenario 9: Societal perspective (included costs of informal care, transportation for hospitalization and health care visits, and patient's productivity loss with event rates)			
BSC	49,639	1.93	
NIN plus BSC	192,823	2.85	155,343

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; FVCPP = forced vital capacity percent predicted; NIN = nintedanib; QALY = quality-adjusted life-year; UIP = usual interstitial pneumonia.

Appendix 5: Submitted Budget Impact Analysis and CADTH Appraisal

Key take-aways of the BIA

- CADTH identified the following key limitations with the sponsor's analysis:
  - Uptake of NIN in the first 3 years was lower than anticipated according to the clinical experts consulted for this review.
  - Prevalence estimates used by the sponsor are uncertain, as is the potential increase in numbers of patients with IPF who will be eligible for NIN under the new PF-ILD indication.
  - The sponsor used the proportion of patients enrolled in public plans, not those eligible for public coverage, to determine the percentage of patients covered in each jurisdiction, which underestimated the potential population size.
  - The proportion of patients over 65 years of age was not aligned with the INBUILD trial.
  - Discontinuation of NIN over 3 years was not considered, which would be expected to reduce the overall budget impact.
  - The assumption that NIN will not displace current use of immunosuppressants was deemed inappropriate by clinical experts consulted by CADTH and is therefore a conservative assumption made by the sponsor.
- CADTH reanalyses included: increasing market uptake of NIN, using the proportion of patients eligible for coverage to calculate market size (rather than those enrolled), and changing the proportion over 65 years of age to align with the INBUILD trial. Based on the CADTH reanalyses, the budget impact from the introduction of NIN is expected to be $4,679,690 in Year 1, $9,490,412 in Year 2, and $14,434,917 in Year 3 with a 3-year total budget impact of $28,605,019 when considering drug costs only.
  - The prevalence of PF-ILD remains a key source of uncertainty in the analysis. Higher estimates are likely to increase the expected budget impact. The budget impact of reimbursing NIN in the UIP-like fibrotic pattern subgroup was estimated to be $13,730,409.
  - CADTH was unable to address limitations regarding the number of IPF patients who are ineligible for NIN under the current IPF indication but may be eligible for NIN under the PF-ILD indication. If these patients were to become eligible for NIN, this would be expected to increase the estimated budget impact. Additionally, CADTH could not account for treatment discontinuation within the budget impact analysis due to the structure of the submitted model, which may reduce the expected budget impact of reimbursing NIN.

Summary of Sponsor's Budget Impact Analysis

The sponsor submitted a budget impact analysis (BIA) estimating the incremental budget impact of reimbursing NIN, in addition to BSC, for the treatment of chronic fibrosing ILD compared to BSC alone from a publicly funded drug plan perspective over a 5-year time horizon. The analytic framework, which used an epidemiology-based approach, leveraged data from multiple sources in the literature and assumptions based on clinical expert input to determine the estimated population size (Table 15). New patients were added to the BIA via an annual average population growth rate that was applied to the entire Canadian population. Key inputs to the BIA are documented in Table 15.

The sponsor only considered patients 25 years of age and over for reimbursement in the analysis. To determine the eligibility of patients for public payer coverage, the sponsor assumed that 50% of the population was between 25 and 65 years of age, and that 50% were over 65 years of age, based on the mean age in the INBUILD trial.[4] The proportion of individuals enrolled in public plans, by jurisdiction and by age subgroups were then applied to derive the eligible patient population size that would be covered by public drug plans. As no fibrosis-targeting treatments are currently approved for PF-ILD, the sponsor assumed that uptake of NIN would not displace current patient use of immunosuppressants and there would be zero costs associated with the reference scenario. Dispensing fees, upcharges, and co-payment deductions were excluded from the sponsor's base-case analysis.

Table 15: Summary of Key Model Parameters

Parameter	Sponsor's estimate (reported as Year 1/Year 2/Year 3[a] if appropriate)[a]
Target population	
Population ≥ 25 years Prevalence of PF-ILD Proportion of patients enrolled in public plans	20,685,233[b] 0.0072%[20] Jurisdiction specific coverage rates were used, stratified by those > 25 years to 65 years and those ≥ 65 years [21]
Number of patients eligible for drug under review	924/936/950
Market uptake (3 years)	
Uptake (reference scenario) Nintedanib	0%/0%/0%
Uptake (new drug scenario) Nintedanib	[redacted]%/ [redacted]%/ [redacted]%
Cost of treatment (per patient)	
Cost of treatment over 1 year Nintedanib	$34,978.05[c]

BIA = budget impact analysis; PF-ILD = progressive fibrosing interstitial lung disease.

[a] The sponsor reported a base case of a 5-year time horizon; however, according to CADTH submission requirements, a 3-year forecast period should be reported in the base case. Longer time horizons may be appropriate if adequate justification provided.

[b] Pan-Canadian (all provinces, minus Quebec).

[c] Annual costs were calculated by weighing the percentage of patients expected to receive the full dose of NIN 150 mg twice daily ([redacted]%) and those receiving a titrated dose of 100 mg twice daily ([redacted]%). Price of NIN was taken from the Ontario Exceptional Access Program. [16]

Source: Sponsor's BIA report.[22]

Summary of the Sponsor's BIA Results

The sponsor estimated the net budget impact of introducing NIN for PF-ILD to be $290,239 in Year 1, $4,022,138 in Year 2, and $7,294,784 in Year 3 for a total budget impact over 3 years of $11,607,161. Note that the sponsor reported a base case with a 5-year total time horizon, although, as per CADTH Common Drug Review submission requirements, only the 3-year total budget impact results are reported.

CADTH Appraisal of the Sponsor's BIA

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the results of the BIA:

- **Uptake of NIN in the first 3 years is lower than anticipated by clinical experts:** According to clinical experts consulted by CADTH for this review, there is significant appetite for use of NIN in the PF-ILD population. Therefore, they felt the sponsor's rate of uptake to be underestimated.
  - In CADTH's reanalyses, the rate of NIN uptake was changed to 10%, 20%, and 30% for years 1, 2, and 3, respectively.
- **Uncertainty in the size of the eligible patient population**: The sponsor's prevalence estimate for PF-ILD was derived from the CARE-PF patient cohort.[20] As noted by clinical experts consulted for this review, the prevalence might be underestimated as only patients receiving care in specialized PF-ILD clinics would have been captured, meaning some patients being managed outside of these specialty clinics would not be accounted for. Further, clinicians noted that ILD is a heterogenous condition, and that PF-ILD is not a diagnosis but rather a description of disease behaviour, highlighting the uncertainty

associated with estimating a prevalence for this indication. As PF-ILD describes a phenotype of diseases, the true prevalence of PF-ILD is difficult to estimate as most epidemiological studies focus on specific ILDs.

Furthermore, according to clinical experts consulted by CADTH, despite NIN being presently indicated for IPF, a proportion of IPF patients do not meet the current eligibility criteria introduced by public drug plans for reimbursement for the IPF indication. With the expanded indication to PF-ILD, some IPF patients who are currently not eligible may become eligible under the PF-ILD indication. If the true prevalence of PF-ILD is higher than the sponsor's estimate and/or if the sponsor's prevalence estimate does not capture those with IPF who are currently ineligible, this would result in a greater budget impact than estimated by both CADTH and the sponsor, should NIN be reimbursed.

  - To explore the influence of alternative PF-ILD prevalence estimates on the results, a prevalence estimate of 8.1 in 100,000 was explored in a scenario analysis.[23] CADTH was unable to address the uncertainty associated with potential indication creep.

- **The market size should be determined by the proportion of patients eligible for public coverage:** To calculate the total percentage of patients covered by public drug plans, the sponsor used the number of patients currently enrolled in public plans for each jurisdiction.[21] It is more appropriate to use the proportion of patients eligible, rather than enrolled, as the market size will be determined by all eligible for public coverage and the BIA should consider all patients eligible whether or not they are presently enrolled. Should NIN be reimbursed by public plans, it is assumed that all eligible patients for this treatment would enroll for public coverage.
  - In CADTH's reanalyses, the proportion eligible was used to determine the market size for NIN. Additionally, as a scenario analysis, all patients were assumed to be covered for NIN regardless of age. If NIN is covered under Exceptional Access Programs (EAP) such as the current situation in Ontario[16], then coverage is expected to be provided to all patients regardless of age.

The proportion of patients over 65 years of age is not aligned with the INBUILD trial: In the sponsor's base case, it was assumed that 50% of patients would be aged 65 or older, based on the average age of patients enrolled.[22] This does not align with the INBUILD trial in which a greater proportion (60.8%) were reported to be 65 years or older.[4]

  - In CADTH reanalyses, the proportion of patients 65 and older were changed to align with the INBUILD trial.

- **Discontinuation of NIN was not considered in the sponsor's BIA**: In the BIA, no patients who initiate NIN discontinue treatment during the 3-year time horizon. According to the CADTH Clinical Review report, 24% of NIN patients discontinued during the 52-week trial. Clinical experts consulted by CADTH also noted that discontinuation of NIN may continue beyond the first year of treatment due to adverse events or disease progression. The CADTH pharmacoeconomic report estimated that 39% of patients would discontinue NIN after 3 years. If patients discontinue NIN within 3 years of initiation, this would decrease the overall budget impact. Therefore, not including discontinuation in the BIA would be a conservative assumption.
  - CADTH could not address this limitation in reanalyses given the structure of the submitted BIA.

- **Inappropriate assumption that immunosuppressants would not be displaced with the reimbursement of NIN**: Clinical experts noted that, at present, immunosuppressants are the only treatment available to patients with PF-ILD. If an antifibrotic treatment were to become available, they would expect this to displace use of immunosuppressants in some patients. If immunosuppressants were displaced upon reimbursement of NIN, this would decrease the overall budget impact.
  - Given the model structure and the lack of evidence informing how immunosuppressant usage may change in patients upon receipt of NIN, CADTH was unable to address this assumption in reanalyses. The cost comparison table in Appendix 1 lists the annual costs associated with the immunosuppressants, which range from $206 to $6,567. As the annual cost of NIN is estimated to be $34,978, the relative cost of immunosuppressants being displaced is lower than that of NIN. If the introduction of NIN were to displace immunosuppressants, the budget impact will likely be less than presently estimated but will not result in cost savings.

CADTH Reanalyses of the BIA

CADTH revised the sponsor's corrected base case by increasing the market uptake over the first 3 years, using the number of patients eligible for public coverage, rather than enrolled, to estimate the percentage of patients who would be covered in each jurisdiction and changing the proportion of patients over 65 years of age to align with the INBUILD trial. Table 16 notes the assumptions used by the sponsor in comparison to those used by CADTH in its reanalysis alongside minor corrections made to the sponsor's model.

Table 16: CADTH Revisions to the Submitted BIA

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
1. Incorrect assignment of the proportion over 65 years	Proportion older than 65 years assigned to "Parameters-Epidemiology" cell C33	Proportion older than 65 years assigned to "Parameters-Epidemiology" cell C34[a]
2. British Columbia's population eligible for public plan enrolment	25 to 64 years: 15,600 65 years and older: 28,900	25 to 64 years: 2,615,600 65 years and older: 849,900
Changes to derive the CADTH base case		
1. Market uptake for years 1, 2, and 3	[redacted]%/ [redacted]%/ [redacted]%	10% / 20% / 30%
2. Percentage of patients covered	Determined by the percentage of patients enrolled	Determined by the percentage of patients eligible for enrolment
3. Proportion 65 years or older	50%	60.8%
CADTH base case		1 + 2 + 3

[a] Allows for correct SUMPRODUCT when C33 and C34 values are multiplied by the proportion of the jurisdictions that are under or over 65.

Applying these changes increased the total 3-year budget impact to $28,605,019 ($30,261,129 including dispensing fees, upcharges, and co-payments). The results of the CADTH step-wise reanalysis are presented in summary format in Table 17 and a more detailed breakdown is presented in Table 18.

Table 17: Summary of the CADTH Reanalyses of the BIA

	3-year total	
Stepped analysis	**Drug costs only**	**Dispensing fees, upcharges, and co-payments included**
Submitted base case	$11,607,161	$12,268,581
Corrected sponsor's base case	$11,607,161	$12,268,581
CADTH reanalysis 1	$19,712,377	$20,835,662
CADTH reanalysis 2	$16,089,908	$17,016,768
CADTH reanalysis 3	$12,974,067	$13,719,243
CADTH base case	$28,605,019	$30,261,129

BIA = budget impact analysis.

CADTH also conducted additional scenario analyses to address remaining uncertainty:

1. Assuming a higher uptake of nintedanib by doubling CADTH's base-case estimates (20%/40%/60%)
2. Assuming a lower uptake of nintedanib by halving CADTH's base-case estimates (5%/10%/15%)
3. Assuming a prevalence for PF-ILD of 8.1 in 100,000,[23] estimated by subtracting the prevalence of IPF (8.2 per 100,000) from the prevalence of fibrotic ILDs (16.3 per 100,000)
4. Assuming 100% of PF-ILD patients would be eligible for public coverage
5. Assuming 62% of the total population had a UIP-like pattern (aligned with the INBUILD trial), and investigating the budget impact if nintedanib was only reimbursed in this subgroup[4]
6. Assuming that 100% of patients will take the full dose (150 mg) of nintedanib
7. Reducing the price of nintedanib to the value in which it would be cost-effective at a $50,000 per QALY threshold (77%)

Results of CADTH's scenario analyses demonstrate that the estimated budget impact is highly sensitive to the prevalence estimate for PF-ILD used and to the expected uptake rate (Table 18). Assuming that all PF-ILD patients would be eligible for public coverage of NIN increased the overall budget impact by approximately $5 million to $33,591,338 over 3 years. Reimbursement of NIN for the subgroup of patients presenting UIP-like fibrotic patterns lowered the estimated budget impact to $13,730,409. At a price reduction of 77% for NIN, this would reduce the estimated budget impact of reimbursement to $6,579,154.

Table 18: Detailed Breakdown of the CADTH Reanalyses of the BIA

		Annual (drug cost only)			3-year total	
Stepped analysis	**Scenario**	**Year 1**	**Year 2**	**Year 3**	**Drug costs only**	**Including dispensing fees, upcharges, co-payments**
Submitted base case	Reference	$0	$0	$0	$0	$0
	New drug	[redacted]	[redacted]	[redacted]	$11,607,161	$12,268,581
	Budget impact	[redacted]	[redacted]	[redacted]	$11,607,161	$12,268,581
CADTH base case	Reference	$0	$0	$0	$0	$0
	New drug	$4,679,690	$9,490,412	$14,434,917	$28,605,019	$30,261,129
	Budget impact	**$4,679,690**	**$9,490,412**	**$14,434,917**	**$28,605,019**	**$30,261,129**
CADTH scenario analysis 1: higher uptake	Reference	$0	$0	$0	$0	$0
	New drug	$9,359,381	$18,980,824	$28,869,833	$57,210,038	$60,522,258
	Budget impact	**$9,359,381**	**$18,980,824**	**$28,869,833**	**$57,210,038**	**$60,522,258**
CADTH scenario analysis 2: lower uptake	Reference	$0	$0	$0	$0	$0
	New drug	$2,339,845	$4,745,206	$7,217,458	$14,302,510	$15,130,565
	Budget impact	**$2,339,845**	**$4,745,206**	**$7,217,458**	**$14,302,510**	**$15,130,565**
CADTH scenario analysis 3: prevalence	Reference	$0	$0	$0	$0	$0
	New drug	$5,264,652	$10,676,714	$16,239,281	$32,180,647	$34,043,770
	Budget impact	**$5,264,652**	**$10,676,714**	**$16,239,281**	**$32,180,647**	**$34,043,770**
CADTH scenario analysis 4: 100% eligibility	Reference	$0	$0	0	$0	$0
	New drug	$5,496,418	$11,146,735	16,954,184	$33,591,338	$35,566,353
	Budget impact	**$5,496,418**	**$11,146,735**	**$16,954,184**	**$33,591,338**	**$35,566,353**
CADTH scenario analysis 5: UIP only	Reference	0	$0	$0	$0	$0
	New drug	2,246,251	$4,555,398	$6,928,760	$13,730,409	$14,525,342
	Budget impact	**$2,246,251**	**$4,555,398**	**$6,928,760**	**$13,730,409**	**$14,525,342**
CADTH scenario analysis 6: 100% 150 mg	Reference	$0	$0	$0	$0	$0
	New drug	$5,553,608	$11,262,717	$17,130,593	$33,946,920	$35,865,710
	Budget impact	**$5,553,608**	**$11,262,717**	**$17,130,593**	**$33,946,920**	**$35,865,710**
CADTH scenario analysis 7: 77% price reduction	Reference	$0	$0	$0	$0	$0
	New drug	$1,076,329	$2,182,795	$3,320,031	$6,579,154	$8,235,264
	Budget impact	**$1,076,329**	**$2,182,795**	**$3,320,031**	**$6,579,154**	**$8,235,264**

BIA = budget impact analysis.

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