Common Drug Review
Pharmacoeconomic Review Report

October 2015

Drug	nintedanib (Ofev)
Indication	For the treatment of idiopathic pulmonary fibrosis (IPF).
Listing request	For adult patients who have a diagnosis of IPF confirmed by a respirologist and a high-resolution computed tomography scan within the previous 24 months with a forced vital capacity ≥ 50% of predicted normal.
Dosage form(s)	100 mg and 150 mg capsules
NOC date	June 25, 2015
Manufacturer	Boehringer Ingelheim Canada Ltd.

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

TABLE OF CONTENTS

Tables

Figures

ABBREVIATIONS

BSC	best supportive care
CDR	CADTH Common Drug Review
CI	confidence interval
FVC	forced vital capacity
ICER	incremental cost-effectiveness ratio
ICUR	incremental cost-utility ratio
IPF	idiopathic pulmonary fibrosis
NMA	network meta-analysis
QALY	quality-adjusted life year

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Nintedanib (Ofev)
Study Question	"To assess the cost-effectiveness of nintedanib versus best supportive care, pirfenidone, and N-acetylcysteine for the treatment of patients with idiopathic pulmonary fibrosis"
Type of Economic Evaluation	Cost-effectiveness analysis and cost-utility analysis
Target Population	Patients with IPF
Treatment	Nintedanib 150 mg twice daily + BSC
Outcomes	• QALYs • Life-years
Comparators	• BSC, represented by control group of phase 3 nintedanib clinical trial (patient monitoring, oxygen, concomitant therapies such as proton pump inhibitors, bronchodilators, antitussives) • Pirfenidone 3 × 267 mg three times daily + BSC • N-acetylcysteine 600 mg three times daily (1,800 mg per day), escalating dose up to 3,142.52 mg daily + BSC
Perspective	Health Canada
Time Horizon	Lifetime (~30 years)
Results for Base Case	Nintedanib versus BSC: $248,000 per QALY Nintedanib versus pirfenidone: nintedanib dominates (less costly and more effective than pirfenidone) Nintedanib versus N-acetylcysteine: $84,000 per QALY
Key Limitations	• One-year trial data (baseline and relative risk of outcomes) extrapolated over a lifetime, with unknown durability of effectiveness over time • Model informed by surrogate outcomes (FVC per cent predicted) • Relative efficacy and safety versus pirfenidone informed by NMA (with no direct comparison and differences in study population between trials)
CDR Estimate(s)	*Nintedanib versus BSC:* • Use of odds ratio from direct evidence instead of NMA, $315,286 per QALY (taken from manufacturer submission) • No improvement in overall survival, $1,273,444 per QALY *Nintedanib versus pirfenidone:* • Best available evidence for nintedanib versus pirfenidone is very uncertain (no direct comparisons, differences in study populations), resulting in inability to determine relative cost-effectiveness with any certainty. • Using a cost minimization approach based on the manufacturer's NMA results — equal efficacy, similar harms (except serious GI events, GI perforation, and skin disorder [photosensitivity and rash]) — nintedanib is $6,356 less costly than pirfenidone (majority of savings from drug cost $6,737). However, as stated above, this result must be interpreted with caution given the uncertainty in comparative clinical effects.

BSC = best supportive care; CDR = CADTH Common Drug Review; FVC = forced vital capacity; GI = gastrointestinal; IPF = idiopathic pulmonary fibrosis; NMA = network meta-analysis; QALY = quality-adjusted life-year.

EXECUTIVE SUMMARY

Background

Nintedanib (Ofev) is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).[1] The manufacturer is requesting listing for patients with IPF confirmed by a respirologist and high-resolution computer tomography scan within the previous 24 months, with a forced vital capacity (FVC) ≥ 50% of predicted normal.[2] The recommended dose is 300 mg daily (150 mg twice daily). The confidential price of nintedanib is $54.36 per 150 mg capsule or $109 per day.

The manufacturer submitted a cost-utility analysis comparing nintedanib plus best supportive care (BSC) versus BSC alone (patient monitoring, oxygen, concomitant therapies such as proton pump inhibitors, bronchodilators, antitussives),[3] assumed to be represented by the control group of the phase 3 nintedanib clinical trials.[4,5] Comparisons with pirfenidone and N-acetylcysteine in adult patients with IPF were also performed over a lifetime time horizon (~30 years) from the perspective of the Canadian health care payer. The risk of survival, exacerbations, and loss of lung function for patients receiving BSC were obtained from TOMORROW[6] and INPULSIS trials,[4,5] and mathematical models were used to estimate long-term efficacy. A manufacturer-conducted network meta-analysis (NMA) was used to estimate relative efficacy and harms among treatments. Quality of life was assigned for each FVC per cent predicted category by compiling data from the INPULSIS trials.[4,5]

Summary of Identified Limitations and Key Results

- *Uncertainty in natural history of disease.* One-year trial data from the BSC group were modelled over a lifetime time horizon (~30 years). While best fit was assessed during this one-year period and face validity was assessed by comparing modelled survival with observational data, alternate parametric models led to major differences in survival (see Appendix 5: FIGURES FROM MANUFACTURER'S SUBMISSION for details). When alternate parametric models are used, the incremental cost-utility ratio (ICUR) of nintedanib versus BSC increases to $370,000 to $721,000 per quality-adjusted life-year (QALY) (from the manufacturer reported base case of $248,000 per QALY).
- *Uncertainty in relative efficacy of nintedanib versus BSC.* The reference case model used the point estimate of survival, which was not statistically significant in either the direct comparison or NMA. When the odds ratio for survival is set to one, in the CADTH Common Drug Review (CDR) analyses, ICUR increases to $1,273,444 per QALY (this may overestimate the ICUR if FVC is a valid surrogate for survival). Note that if direct comparison results are used (instead of NMA results), the ICUR of nintedanib versus BSC increases to $315,286 per QALY.
- *Uncertainty in relative efficacy of nintedanib versus pirfenidone.* The relative efficacy and safety of nintedanib versus pirfenidone is very uncertain. The manufacturer-conducted NMA lacks any direct comparisons, and there are differences in the characteristics of study populations. Results of this NMA largely show no differences in efficacy and harms, but with wide confidence intervals. This uncertainty is a major limitation as pirfenidone may be the most appropriate comparator in Canada.
- *Uncertainty in long-term efficacy.* The manufacturer assumed that differences in outcomes observed in short-term randomized controlled trials (12-month) can be extrapolated to a lifetime time horizon. If efficacy attenuates over time, the ICUR of nintedanib versus BSC would be underestimated.
- *Overestimate of resource use with skin disorder.* The manufacturer used the cost of a hospital admission for skin disorder (photosensitivity and rash) as a representative cost ($1,800); however, admission would be a very uncommon event. By lowering the skin disorder cost to represent

outpatient management in the manufacturer's base case, nintedanib still dominates but the cost saving is slightly lower (from $12,735 to $11,369).

CADTH Common Drug Review Revised Reference Case and Exploration of Uncertainty

Nintedanib versus BSC

- Use of direct comparison results (versus NMA): ICUR increases to $315,286 per QALY.
- No mortality benefit (odds ratio for mortality crosses unity in direct comparison): ICUR increases to $1,273,444 per QALY. Note that if FVC is a valid surrogate for mortality, this may overestimate the ICUR (underestimate survival benefit).

Nintedanib versus pirfenidone

- Cost minimization analysis assuming equal efficacy, similar harms (except serious gastrointestinal events, gastrointestinal perforation, and skin disorder [photosensitivity and rash], the latter with lower cost): nintedanib is less costly by $6,356 (saving from treatment $6,737; additional adverse event cost of $380). Note that the assumption that nintedanib has similar efficacy to pirfenidone has not yet been definitely established and cannot be assumed based on the weak clinical evidence available.

Conclusions

The manufacturer base case suggests that nintedanib results in an additional 0.3541 QALYS compared with BSC, but is $86,000 more costly, driven primarily by drug acquisition costs. The manufacturer-stated ICUR is $248,186 per QALY. When compared with pirfenidone, nintedanib dominates pirfenidone due to lower drug acquisition cost ($9 less per day).

The ICUR in the CDR reference case increases dramatically when direct evidence is used to inform the model and when nintedanib is assumed to result in similar survival compared to BSC ($315,000 to $1.3 M per QALY). There is significant uncertainty in the model, particularly surrounding long-term baseline and relative risk of death. If true relative efficacy is less than estimated, the ICUR will be even higher.

There is limited comparative clinical information for nintedanib and pirfenidone — no evidence of improved efficacy for nintedanib compared with pirfenidone, and no strong evidence that nintedanib is non-inferior to pirfenidone. When comparing drug costs, nintedanib results in small cost savings, with an annual cost that is 93% to 95% of pirfenidone. Note that the Canadian Drug Expert Committee recommended a substantial price reduction for pirfenidone; true differences in drug cost may differ.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer conducted a cost-utility analysis comparing nintedanib to best supportive care (BSC), pirfenidone, and N-acetylcysteine.[3] The model used data from two phase 3 nintedanib clinical trials (INPULSIS[4,5]) to inform baseline model probabilities of events (for the BSC strategy) and conducted a network meta-analysis (NMA) for relative efficacy and safety. The reference model time horizon was the patient's lifetime, using the Canadian public payer perspective. The economic submission is based on a long-term Markov model comprised of 17 health states (eight levels of lung functions without exacerbation; eight levels of lung functions with exacerbation; and death).

In the three-month-cycle Markov model, patients with idiopathic pulmonary fibrosis (IPF) enter the model at different lung functions (by category of forced vital capacity [FVC] per cent predicted) without exacerbation, with a distribution based on INPULSIS participants. Within each Markov cycle, patients can experience loss of lung function (progression to a health state with lower FVC per cent predicted), exacerbation, loss of lung function combined with exacerbation, remaining in the same health state, or death. Adverse events, including serious cardiac events, serious gastrointestinal events, photosensitivity, and gastrointestinal perforation, were also considered in the model based on rates observed from the clinical trials and literature.[7,8]

The baseline risks of mortality, disease progression, and acute exacerbations for patients receiving BSC were derived from patients in the placebo group of three clinical trials (phase 2 TOMORROW trial[6] and two phase 3 INPULSIS trials[4,5]). The risk of events was extrapolated beyond the observed trial period of 12 months over a lifetime using parametric models. The relative effectiveness and safety of nintedanib, pirfenidone, and N-acetylcysteine were obtained from a manufacturer-conducted NMA that included outcomes of survival, disease progression by FVC per cent predicted, exacerbations, discontinuation, and adverse events. Quality of life for each FVC per cent predicted health state and disutilities related to acute exacerbation and serious gastrointestinal events were informed by the patient-level EuroQol 5-Dimensions Questionnaire (EQ-5D) data from the INPULSIS trials (by event and not treatment allocation). Adverse event–related disutilities such as serious cardiac events, skin disorders, and gastrointestinal perforation were estimated from published literature.[9] Costs, including treatment-related costs, drug acquisition costs, treatment-related adverse events costs, liver function test costs, concomitant medications, background follow-up costs (including hospitalization), oxygen use costs, exacerbation costs, and end-of-life costs, were provided by the manufacturer and based on resource use from INPULSIS trials and cost from Canadian sources.[3]

2. MANUFACTURER'S BASE CASE

This report focuses on the comparison between nintedanib versus BSC and nintedanib versus pirfenidone, as N-acetylcysteine is not a standard-of-care treatment for IPF in Canada. For information on nintedanib versus N-acetylcysteine, please refer to Appendix 5: FIGURES FROM MANUFACTURER'S SUBMISSION.

Nintedanib versus BSC

In its reference case, the manufacturer reported that nintedanib compared with BSC is associated with a cost per quality-adjusted life-year (QALY) of $248,186 or a cost per life-year of $200,327.

TABLE 2: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE (NINTEDANIB VERSUS BSC)

	BSC	NTB	Incremental
Total Cost ($)	44,390	132,273	87,883
• Treatment cost ($)	0	85,642	85,642
• Adverse event ($)	2,610	3,203	593
• Liver panel test ($)	0	70	70
• Patient monitoring and O_2 use ($)	31,991	34,425	2,434
• Acute exacerbation costs ($)	6,637	5,843	–795
• End-of-life costs ($)	3,152	3,091	–60
Total QALYs	3.0995	3.4536	0.3541
Total LYs	4.1201	4.5588	0.4387
ICUR ($/QALY)			248,186
ICER ($/LY)			200,327

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; LY = life-year; NTB = nintedanib;
QALY = quality-adjusted life-year.
Source: Manufacturer's pharmacoeconomic submission,[3] page 76.

Nintedanib versus pirfenidone

When comparing nintedanib with pirfenidone, nintedanib dominates (less costly and more effective).

TABLE 3: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE (NINTEDANIB VERSUS PIRFENIDONE)

	PFN	NTB	Incremental
Total Cost ($)	145,008	132,273	–12,735
• Treatment cost ($)	94,951	85,642	–9,309
• Adverse event ($)	4,604	3,203	–1,401
• Liver panel test ($)	72	70	–2
• Patient monitoring and O_2 use ($)	34,883	34,425	–458
• Acute exacerbation costs ($)	7,404	5,843	–1,562
• End-of-life costs ($)	3,094	3,091	–3
Total QALYs	3.4104	3.4536	0.0432
Total LYs	4.5566	4.5588	0.0022
ICUR ($/QALY)			NTB dominates[a]
ICER ($/LY)			NTB dominates

ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; LY = life-year; NTB = nintedanib;
PFN = pirfenidone; QALY = quality-adjusted life-year.
[a] NTB dominates = NTB is less costly and more effective (more QALYs or LYs) compared with PFN.
Source: Manufacturer's pharmacoeconomic submission,[3] page 88.

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

Uncertainty was addressed using Monte Carlo simulation and one-way deterministic sensitivity analyses, which varied model parameters by using alternative values. A series of one-way sensitivity analyses was conducted by the manufacturer, including alternate parametric models to estimate mortality, exacerbations, progression, discontinuation and adverse events (95% confidence interval [CI]); costs for treatment, follow-up, oxygen use, end of life, and adverse events (95% CI); utilities (95% CI); and overall survivals, acute exacerbations, loss of lung function, safety, discontinuation, and FVC per cent predicted categories (different model assumptions).

Nintedanib versus BSC

The reference case result for nintedanib versus BSC is $248,186 per QALY.

The following parameters increased or decreased the incremental cost per QALY gained by more than 25%:

- 95% CI of odds ratio of mortality: cost per QALY $148,676 to BSC dominant (nintedanib more costly and less effective than BSC)
- Changed the baseline survival risk from loglogistic to Weibull: cost per QALY $378,264
- Changed the baseline survival risk from loglogistic to Gompertz: cost per QALY $720,969
- Used direct evidence (outcomes of survival, exacerbation, loss of lung function, and discontinuation) instead of NMA for nintedanib: cost per QALY $315,286.

According to the cost acceptability curve from the probabilistic sensitivity analyses, 50% of the incremental cost-effectiveness ratios (ICERs) would fall below the $240,000 per QALY threshold for nintedanib versus BSC; 0% of the ICERs would fall below $100,000 per QALY threshold.

Nintedanib versus pirfenidone

In the reference case, nintedanib was dominant (less costly and associated with more QALYs and life-years).

The following parameter increased or decreased the incremental cost per QALY gained by more than 25%:

- Imposed a stopping rule on pirfenidone (discontinuation and loss of treatment effect for pirfenidone patients that showed a loss of lung function of at least 10% in FVC per cent predicted; not applied to nintedanib group): cost per QALY was $85,457. The clinical expert indicated that pirfenidone is commonly discontinued if there is no efficacy or loss of efficacy; while not known, it is likely that nintedanib would be used in a similar manner, so this analysis may overestimate the incremental cost-utility ratio (ICUR).

For the reference case, according to the cost acceptability curve from the probabilistic sensitivity analyses, nintedanib dominates pirfenidone in 70% of the model simulations (less costly, more effective).

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

- *Uncertainty in natural history of disease.* One-year trial data from the BSC group were modelled over a lifetime time horizon. While best fit is assessed during this one-year period and face validity assessed by comparing modelled survival with observational data (three years), alternate parametric models lead to major differences in survival (see Appendix 5: FIGURES FROM MANUFACTURER'S SUBMISSION for details). When alternate parametric models are used, the ICUR of nintedanib versus BSC increases to $370,000 to $721,000 per QALY.
- *Uncertainty in relative efficacy of nintedanib versus BSC.* The reference case model uses the point estimate of survival, which is not statistically significant in either the direct comparison or NMA. Note that if direct comparison results are used (instead of NMA results), the ICUR of nintedanib versus BSC increases to $315,286 per QALY. In the CADTH Common Drug Review (CDR) analyses where the odds ratio on survival is equal to 1, ICUR is $1,273,444 per QALY.
- *Uncertainty in long-term efficacy.* The model assumes that differences in outcomes observed in short-term randomized controlled trials (12-month) can be extrapolated to a lifetime time horizon. If efficacy attenuates over time the ICUR of nintedanib versus BSC may be underestimated.
- *Uncertainty in treatment discontinuation and its effect.* Odds ratios from the NMA are estimated based on the discontinuation rate in the first 12 months of the trials and are applied in the model for lifetime, resulting in a lower and lower proportions of patients in the nintedanib strategy taking the drug. This may lead to optimistic mortality estimates over time.
- *Lack of direct evidence for relative safety and efficacy of nintedanib versus pirfenidone.* Relative efficacy between nintedanib and pirfenidone is estimated using NMA, and no direct evidence is available. All the confidence intervals (except gastrointestinal events) from the NMA cross unity; therefore, there is no clear benefit of one drug over the other. CDR has performed a cost minimization analysis assuming the effectiveness and safety profile of the two drugs are the same. It should also be noted, however, that the finding of the NMA cannot establish non-inferiority of the two drugs.
- *Overestimate of cost of skin disorder.* The manufacturer estimated the cost of skin disorder (photosensitivity and rash) with pirfenidone to be equivalent to the cost of treating this condition as an inpatient. However, a very small proportion of individuals (if any) would be treated as inpatients. If costs are changed to approximate outpatient treatment in the manufacturer's base case, nintedanib still dominates, but the cost saving is slightly lower (from $12,735 to $11,369).

5. CADTH COMMON DRUG REVIEW ANALYSES

CDR considered the following analyses to address the identified limitations.

Nintedanib versus BSC

- Change odds ratio of survival to 1.0 (base case 0.70, CI 0.45 to 1.1), incremental cost = $77,099 and incremental QALYs = 0.0433, ICUR = $1,273,444 per QALY.
- Change odds ratio of adverse cardiac events to 1 (base case 0.92, CI 0.53 to 1.63), incremental cost = $87,976 and incremental QALYs = 0.3536, ICUR = $248,766 per QALY.
- Change odds ratio to 1 for all non-significant events (survival and cardiac events), incremental cost = $77,184 and incremental QALYs = 0.0432, ICUR = $1,283,729 per QALY.
- Short time horizon. To assess the timing of accrual of benefits and costs, shorter time horizons were explored. Note that in the reference case incremental QALY is 0.3541.
  - One year: Incremental cost = $30,062 and incremental QALY = 0.0047; ICUR = $6,396,077
  - Three years: Incremental cost = $66,240 and incremental QALY = 0.0728; ICUR = $909,484
  - Five years: Incremental cost = $79,066 and incremental QALY = 0.1609; ICUR = $491,400.

Nintedanib versus pirfenidone

- The only available (indirect) evidence does not suggest that significant differences exist for efficacy and harms of nintedanib versus pirfenidone for most outcomes. If the odds ratios for nintedanib and pirfenidone are equal for survival, exacerbations, loss of lung function, discontinuation, and serious cardiac events, the cost saving from nintedanib is $7,685 (saving from treatment $6,736 and from adverse events $949).
- Keeping the same odds ratio as above and excluding costs on skin disorder and gastrointestinal perforation: the cost saving from nintedanib is $6,451 (saving from treatment $6,732 but additional adverse event cost of $281).
- Keeping the same odds ratio as above and using lower costs for skin disorder (from $1,806 to $116.6, which includes a dermatologist consultation [A025] and a repeat consultation [A026], based on the Ontario Schedule of Benefits [date not stated]): the cost saving from nintedanib is $6,356 (saving from treatment $6,737 but additional adverse event cost of $380).

Note: Cost minimization analysis is adopted for nintedanib versus pirfenidone, as the estimates from the NMA are mostly insignificant. After odds ratios are set to equal, there is minimal QALY difference (< 0.02, approximately seven days of perfect health) in the model because of the underlying adverse events (serious gastrointestinal events, skin disorders, and gastrointestinal perforation). CDR has decided to focus on the treatment and adverse event costs where the two drugs differ. Note, however, that given the poor quality of the underlying data, it is uncertain if nintedanib is “as effective” as pirfenidone.

TABLE 4: SUMMARY OF CADTH COMMON DRUG REVIEW RESULTS (NINTEDANIB VERSUS PIRFENIDONE)

	PFN	NTB	Incremental
Scenario 1 (Same OR)			
Total Cost ($)[a]	139,958	132,273	–7,685
• Treatment cost ($)	92,378	85,642	–6,737
• Adverse event ($)	4,151	3,203	–949
• Liver panel test ($)	70	70	0
• Patient monitoring and O_2 use ($)	34,425	34,425	0
• Acute exacerbation costs ($)	5,843	5,843	0
• End-of-life costs ($)	3,091	3,091	0
Total QALYs	3.4387	3.4536	0.0149
Scenario 2 (Same OR, No Skin Disorder and GI Perforation)			
Total Cost ($)	138,444	131,993	–6,451
• Treatment cost ($)	92,318	85,586	–6,732
• Adverse event ($)	2,729	3,010	281
Total QALYs	3.4524	3.4513	–0.0011
Scenario 3 (Same OR, Lower Skin Disorder Cost)			
Total Cost ($)	138,629	132,273	–6,356
• Treatment cost ($)	92,378	85,642	–6,737
• Adverse event ($)	2,822	3,203	380
Total QALYs	3.4387	3.4536	0.0149

GI = gastrointestinal; NTB = nintedanib; OR = odds ratio; PFN = pirfenidone; QALY = quality-adjusted life-year.
[a] For cost minimization analysis, only treatment cost and adverse event costs are different between the two drugs. Other costs stay the same as in Scenario 1.

TABLE 5: CADTH COMMON DRUG REVIEW REANALYSIS PRICE REDUCTION SCENARIOS

ICURs of NTB Versus BSC		
Price	**Base-Case Analysis Submitted by Manufacturer**	**Reanalysis by CDR, Based On Same OR of Survival**
Submitted	**248,186**	**1,273,444**
10% reduction	224,005	1,143,207
20% reduction	199,824	1,012,971
30% reduction	175,621	882,615
40% reduction	151,440	752,379
50% reduction	127,258	622,143
60% reduction	103,077	491,907
70% reduction	78,896	361,671
80% reduction	54,693	231,315
90% reduction	30,512	101,079

BSC = best supportive care; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; NTB = nintedanib; OR = odds ratio.

Price reduction scenarios are not available for nintedanib versus pirfenidone, as the daily cost for nintedanib is lower than pirfenidone. However, Table 6 shows the relative drug acquisition costs (daily drug costs) of nintedanib and pirfenidone if the same percentage of reduction is applied. This will allow jurisdictions to know how much price reduction is needed for nintedanib if pirfenidone is funded. Note that based on annual costs, nintedanib is 93% to 95% of the cost of pirfenidone.

TABLE 6: CADTH COMMON DRUG REVIEW REANALYSIS RELATIVE DRUG ACQUISITION COST

Relative Drug Acquisition Cost of NTB Versus PFN (Daily Cost)		
	NTB	PFN
Submitted price	**108.72**	**117.27**
10% reduction	97.85	105.54
20% reduction	86.98	93.82
30% reduction	76.10	82.09
40% reduction	65.23	70.36
50% reduction	54.36	58.64
60% reduction	43.49	46.91
70% reduction	32.62	35.18
80% reduction	21.74	23.45
90% reduction	10.87	11.73

CDR = CADTH Common Drug Review; NTB = nintedanib; PFN = pirfenidone.

The manufacturer also claimed that pirfenidone should be considered the most clinically relevant alternative to nintedanib due to the positive market authorization and reimbursement. Pirfenidone is currently listed as a restricted benefit with specified clinical criteria in a number of jurisdictions (Manitoba, Ontario, New Brunswick, Nova Scotia, Prince Edward Island, Newfoundland and Labrador, and Yukon). There is also exceptional drug access for the federal Non-Insured Health Benefits Program. According to the clinical expert, only a small proportion of IPF patients are currently on pirfenidone but the number is growing.

6. ISSUES FOR CONSIDERATION

The Canadian Drug Expert Committee has recommended that pirfenidone be listed for the treatment of adults with mild to moderate IPF, under the condition of a substantial price reduction. The actual price drug plans pay may not be represented in the manufacturer-conducted analysis.

The use of nintedanib in patients who have not tolerated or not responded to treatment with pirfenidone has not been studied, and the cost-effectiveness is unclear. If sequential use of these two drugs is allowed, the total drug costs for treatment of IPF may increase considerably.

7. PATIENT INPUT

Patients report the significant impact IPF has on their quality of life, mental well-being, and activities of daily living, particularly as the disease progresses. Quality of life, including with progressed disease, is incorporated into the economic model. Patients also report the impact on families and primary caregivers, although societal perspective was not assessed in the submission. Patients also expect nintedanib to offer them an alternative medication choice if current treatment is not well tolerated.

8. CONCLUSIONS

The manufacturer's base case suggests that nintedanib results in an additional 0.3541 QALYs compared with BSC but is $86,000 more costly, driven primarily by drug acquisition costs. The manufacturer-stated ICUR is $248,186 per QALY. When compared with pirfenidone, nintedanib dominates pirfenidone due to lower drug acquisition cost ($9 less per day).

The ICUR in the CDR reference case increases dramatically when nintedanib no longer improves survival when compared with BSC ($315,000 to $1.3 M per QALY). There is significant uncertainty in the model, particularly surrounding long-term relative efficacy on overall survival. If true relative efficacy is less than estimated, the ICUR will be even higher.

Nintedanib results in small cost savings in drug acquisition cost, with an annual cost that is 93% to 95% of pirfenidone. Note that the Canadian Drug Expert Committee recommended a substantial price reduction for pirfenidone; true differences in drug cost may differ. It is not clear that the cost of adverse events differs substantially between nintedanib and pirfenidone. Further, there is no strong evidence that nintedanib has improved efficacy versus pirfenidone or that nintedanib is truly non-inferior to pirfenidone.

APPENDIX 1: COST COMPARISON

The comparators presented in Table 7 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice rather than actual practice. Comparators are not restricted to drugs but may be devices or procedures. Costs are manufacturer list prices unless otherwise specified.

TABLE 7: COST COMPARISON TABLE FOR PIRFENIDONE

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Use	Average Cost per Year ($)
Nintedanib (Ofev)	**100 mg 150 mg**	**cap**	**27.1800[a] 54.3600[a]**	**150 mg twice daily**	**39,683**
Pirfenidone (Esbriet)	267 mg	cap	13.0302[b]	Days 1 to 7: one cap, three times a day (801 mg/day) Days 8 to 14: two caps, three times a day (1,602 mg/day) Day 15 onward: three caps, three times a day (2,403 mg/day)	First year: 41,983 Subsequent years: 42,804
Non-Indicated Therapy[c]					
N-acetylcysteine (generic)	200 mg/mL vial	10 mL 30 mL	6.0300[d] 14.7800[d]	3 mL to 5 mL by nebulizer 3 to 4 times daily	1,618 to 3,596

cap = capsule; ODB = Ontario Drug Benefit; RAMQ = Régie de l'assurance maladie du Québec.
[a] Manufacturer's submitted and marketed price.
[b] ODB Exceptional Access Program list price (May 2015).[10]
[c] Indication: "As a mucolytic drug: Acetylcysteine is indicated as adjuvant therapy for patients with abnormal, viscid or inspissated mucous secretions in such conditions as: chronic bronchopulmonary disease such as emphysema, chronic bronchitis, lung abscess, tuberculosis, bronchiectasis, and primary amyioidosis of the lung; acute bronchopulmonary disease such aspneumonia, bronchitis and tracheobronchitis; pulmonary complications of cystic fibrosis; tracheostomy care, pulmonary complications associated with surgery; use during anesthesia; post-traumatic chest conditions and pulmonary collapse; diagnostic bronchial studies such as bronchograms, bronchospirometry and bronchial wedge catheterization."
[d] RAMQ liste des médicaments price (May 2015).[11]

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 8: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS NINTEDANIB RELATIVE TO BEST SUPPORTIVE CARE?

NTB Versus BSC	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation	$248,186 per QALY $200,327 per life-year					

BSC = best supportive care; CE = cost-effectiveness; NA = not applicable; NTB = nintedanib; QALY = quality-adjusted life-year.

TABLE 9: WHEN CONSIDERING ONLY COSTS, OUTCOMES, AND QUALITY OF LIFE, HOW ATTRACTIVE IS NINTEDANIB RELATIVE TO PIRFENIDONE?

NTB Versus PFN	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)		X				
Drug treatment costs alone		X				
Clinical outcomes			X			
Quality of life			X			
Incremental CE ratio or net benefit calculation	NTB dominates					

CE = cost-effectiveness; NA = not applicable; NTB = nintedanib; PFN = pirfenidone.

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 10: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?	X		
Comments	None		
Was the material included (content) sufficient?	X		
Comments	None		
Was the submission well organized and was information easy to locate?	X		
Comments	None		

TABLE 11: AUTHOR INFORMATION

Authors of the Pharmacoeconomic Evaluation Submitted to CDR
☐ Adaptation of global model/Canadian model done by the manufacturer
☒ Adaptation of global model/Canadian model done by a private consultant contracted by the manufacturer
☐ Adaptation of global model/Canadian model done by an academic consultant contracted by the manufacturer
☐ Other (please specify)

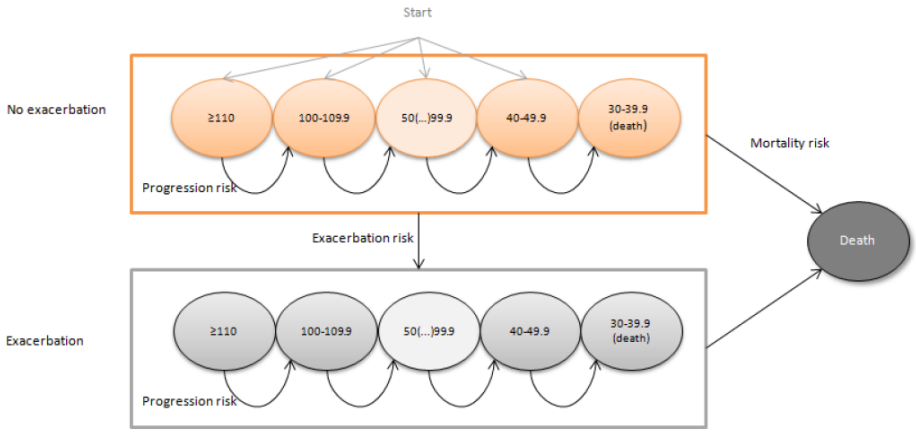
	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document		X	
Authors had independent control over the methods and right to publish analysis			X

APPENDIX 4: REVIEWER WORKSHEETS

Manufacturer's Model Structure

In the three-month-cycle Markov model, patients with idiopathic pulmonary fibrosis (IPF) enter the model at different lung function states (by categories of forced vital capacity [FVC] per cent predicted) without exacerbation, with the distribution of patients in each FVC per cent predicted health state based on the INPULSIS trials. Within each Markov cycle, they can experience loss of lung function (progression to a health state with lower FVC per cent predicted), exacerbation, loss of lung function combined with exacerbation, remaining in the same health state, or death (Figure 1). Adverse events, including serious cardiac events, serious gastrointestinal events, photosensitivity, and gastrointestinal perforation, were also considered in the model, with probabilities of these events obtained from the clinical trials and literature.[7,8]

FIGURE 1: HEALTH STATES IN MANUFACTURER MODEL



Source: Manufacturer's pharmacoeconomic submission,[3] page 17.

Model validation was conducted by the manufacturer for the parameters of survival, exacerbation, and distribution of patients in FVC per cent predicted categories. The three different approaches to extrapolating survival from short-term trials to 10-year survival (Gompertz, loglogistic, and Weibull) were compared with the extracted Kaplan–Meier curves from the three-year Kondoh study (observational data).[12] A loglogistic model was chosen for the base-case analysis because it was closer to the no-exacerbation cohort of the Kondoh study. Validation was also performed for the exacerbation model against the Kaplan–Meier curves from the one-year clinical trial. The distribution of the patients in FVC per cent predicted categories after one year in the model was also compared with the clinical trial results.

TABLE 12: DATA SOURCES

Data Input	Description of Data Source	Comment
Mortality	Pooled phase 2 clinical trial (TOMORROW) and phase 3 (INPULSIS) clinical trials data were used for BSC risk. Parametric survival analysis (loglogistic) was conducted to predict long-term survival. NMA OR values were then applied for nintedanib, pirfenidone, and N-acetylcysteine.	Uncertainty in both short-term (OR cross unity) and long-term efficacy for nintedanib, pirfenidone, and N-acetylcysteine.
Loss of lung function (disease progression)	Phase 3 (INPULSIS) clinical trials data were used in a logistic model to estimate the probability of progression for the BSC FVC per cent predicted category. NMA OR values were used for nintedanib, pirfenidone, and N-acetylcysteine.	Uncertainty in true long-term efficacy for nintedanib, pirfenidone, and N-acetylcysteine.
Exacerbation	Parametric survival analysis (exponential) was conducted to predict long-term exacerbation using phase 3 (INPULSIS Studies 1199.32 and 1199.34) clinical trials data for BSC risk. NMA OR values were used for nintedanib, pirfenidone, and N-acetylcysteine.	Uncertainty in true long-term efficacy for nintedanib, pirfenidone, and N-acetylcysteine. The exponential extrapolation favours nintedanib in the CE analysis.
Adverse events (serious cardiac and GI events, skin disorder, and GI perforation)	The risks of serious cardiac events and serious GI events were obtained from the INPULSIS trials for BSC. NMA OR values were used for nintedanib, pirfenidone, and N-acetylcysteine. GI perforation events for BSC and nintedanib were obtained from FDA nintedanib prescribing information. Risk of skin disorder (photosensitivity and rash) for BSC and pirfenidone were obtained from NICE.	Skin disorder and GI perforation were not included in the NMA and no data were available on how nintedanib was compared with pirfenidone on these events. The true relative impacts of these events are not clear.
Treatment discontinuation	The probabilities of discontinuation for the active treatments (nintedanib, pirfenidone, and N-acetylcysteine) were estimated via OR values obtained from the NMA, assuming a constant risk over time. Discontinuation rates for nintedanib and pirfenidone are quite high.	High discontinuation leads to lower drug costs, but it appears that the model assumes that relative efficacy (1 year) continues over time, which may not occur.
Utilities	Patient-level EQ-5D data collected as part of the INPULSIS clinical trials (i.e., post-hoc analysis of INPULSIS data) were used in the base-case analysis for lung function, exacerbation, and serious GI events. Other adverse event–related disutilities were obtained from published literature.	Appropriate. Note that available data do not indicate difference in QoL by treatment (nintedanib versus BSC).
Costs		
Drug	Cost per pill from manufacturer and OMHTLC	
AEs	The cost of treating myocardial infarction was used for cost of serious cardiac event. The cost of treating a serious GI event was equivalent to the cost of diarrhea (gastroenteritis and colitis), nausea, and dehydration. Photosensitivity reaction was assumed equivalent to the average cost of treating photodermatitis, rash, and other	The manufacturer estimated the cost of photosensitivity with pirfenidone to be equivalent to the cost of treating this condition as an inpatient. However, a very small proportion of individuals (if any) would be treated as inpatients. No data were provided

Data Input	Description of Data Source	Comment
	nonspecific skin eruption and one dermatology visit treated in hospital (LOS 3.3 days). The cost of GI perforation was represented by the cost of non-traumatic intestine perforation. Costs were obtained from OCCI and OSB.	to support the need for admission.
Liver function tests	Liver function tests (liver panel blood test) were assumed to be routinely performed for patients on nintedanib and pirfenidone, and the cost was obtained from OSLB.	
Concomitant medications	The medications used and the respective incidences were obtained from the pooled INPULSIS data. Unit cost of each drug was obtained from ODB.	
Background follow-up	Includes hospitalizations, ERs, GP, and specialists, and procedures for each FVC per cent predicted category. The INPULSIS data informed the probability, resource use, and intensity while the OMHLTC informed the unit cost.	
Oxygen use	Assumed that patients who drop below 80% would require oxygen supplementation as suggested by NICE guidelines. Cost of oxygen supplementation was estimated from OSPB.	
Acute exacerbation	Data from INPULSIS were analyzed to calculate 3-month probabilities of visiting the hospital, using an ER, visiting a GP, and visiting a specialist following an acute exacerbation event. OMHLTC informed the unit cost.	
End of life	A retrospective study of Canadians with COPD was used to inform health utilization (Goodridge et al. 2008).	Appropriate

BSC = best supportive care; CE = cost-effectiveness; COPD = chronic obstructive pulmonary disease; EQ-5D = EuroQoL 5-Dimensions Questionnaire; ER = emergency room; FVC = forced vital capacity; GI = gastrointestinal; GP = general practitioner; LOS = length of stay; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; OCCI = Ontario Case Costing Initiative; ODB = Ontario Drug Benefit; OSLB = Ontario Schedule of Laboratory Benefits; OSPB= Ontario Schedule of Physician Benefits; OMHLTC = Ontario Ministry of Health and Long-Term Care; OR = odds ratio; QoL = quality of life.

TABLE 13: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
The model assumed FVC per cent predicted as the primary driver of disease progression.	Reasonable assumption, but there is a lack of high-quality data in this disease to be a definitively valid surrogate.
It was assumed that once progressed to a lower FVC per cent predicted, the cohort could not regress back to health states with improved lung function (higher FVC per cent predicted). Moreover, once an exacerbation occurred, the cohort could not move back to a health state without exacerbation and would continue in the health states with exacerbation history.	Reasonable assumption.
Extrapolation of the INPULSIS trials using parametric survival analysis was assumed to represent long-term survival with best supportive care.	Reasonable; however, alternate parametric models lead to major differences in survival, particularly in later years of the model.
Patients reaching a level of FVC per cent predicted of 30% were assumed to be at an unsustainable level of lung function (death).	Reasonable.
The economic model assumed that patients who experienced at least one exacerbation event are at risk of recurrent events. Due to lack of evidence on the incidence of recurrent events the model assumed the same risk as for patients that have not had an exacerbation.	Uncertain.
The model assumed that when liver enzyme elevations were detected, they contributed only to the overall discontinuation from treatment, and that there was no disutility or additional costs associated with them.	Reasonable.
Assumed no discontinuation from BSC.	Reasonable.

BSC = best supportive care; FVC = forced vital capacity.

Manufacturer's Results

TABLE 14: DISAGGREGATED REFERENCE CASE RESULTS

	BSC	NDB	Incremental
Treatment costs	$0.00	$85,641.67	$85,641.67
Adverse event costs	$2,609.59	$3,202.51	$592.92
Liver panel tests	$0.00	$69.92	$69.92
Patient monitoring and O_2 use	$31,990.92	$34,424.93	$2,434.01
Acute exacerbation costs	$6,637.25	$5,842.55	-$794.70
End of life costs	$3,151.83	$3,091.42	-$60.41
Total costs	**$44,389.59**	**$132,273.01**	**$87,883.42**
Total QALYs	**3.0995**	**3.4536**	**0.3541**
LYs	4.1201	4.5588	0.4387
Exacerbation events	0.3081	0.2712	-0.0369
Net monetary benefit	$265,556.33	$213,083.19	
Cost-effectiveness	$14,321.72	$38,300.46	
ICER (per QALY)			**$248,186.18**
ICER (per LY)			$200,327.46
ICER (per exacerbation avoided)			$2,382,600.47

	PFN	NDB	Incremental
Treatment costs	$94,950.79	$85,641.67	-$9,309.12
Adverse event costs	$4,603.98	$3,202.51	-$1,401.47
Liver panel tests	$71.87	$69.92	-$1.95
Patient monitoring and O_2 use	$34,882.58	$34,424.93	-$457.64
Acute exacerbation costs	$7,404.39	$5,842.55	-$1,561.84
End of life costs	$3,094.14	$3,091.42	-$2.72
Total costs	**$145,007.75**	**$132,273.01**	**-$12,734.74**
Total QALYs	**3.4104**	**3.4536**	**0.0432**
LYs	4.5566	4.5588	0.0022
Exacerbation events	0.3437	0.2712	-0.0725
Net monetary benefit	$196,027.28	$213,083.19	
Cost-effectiveness	$42,519.90	$38,300.46	
ICER (per QALY)			**NDB dominates**
ICER (per LY)			-$5,837,216.69
ICER (per exacerbation avoided)			-$175,670.55

	NAC	NDB	Incremental
Treatment costs	$4,909.72	$85,641.67	$80,731.95
Adverse event costs	$5,683.79	$3,202.51	-$2,481.27
Liver panel tests	$54.32	$69.92	$15.60
Patient monitoring and O_2 use	$24,042.57	$34,424.93	$10,382.36
Acute exacerbation costs	$4,992.12	$5,842.55	$850.43
End of life costs	$3,260.25	$3,091.42	-$168.83
Total costs	**$42,942.76**	**$132,273.01**	**$89,330.24**
Total QALYs	**2.3939**	**3.4536**	**1.0597**
LYs	3.1837	4.5588	1.3751
Exacerbation events	0.2317	0.2712	0.0395
Net monetary benefit	$196,444.10	$213,083.19	
Cost-effectiveness	$17,938.65	$38,300.46	
ICER (per QALY)			**$84,298.20**
ICER (per LY)			$64,963.26
ICER (per exacerbation avoided)			-$2,263,098.27

BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life-year; NAC = N-acetylcysteine; NDB = nintedanib; PFN = pirfenidone; QALY = quality-adjusted life-year.
Source: Manufacturer's pharmacoeconomic submission,[3] pages 76, 88, 96.

CADTH Common Drug Review Reanalysis

Given the non-significant odds ratios from the network meta-analysis (NMA), these were assessed in the following reanalyses:

Nintedanib versus best supportive care

- Change odds ratio of survival to 1.0 (base case 0.70, confidence interval [CI] 0.45 to 1.1), incremental cost = $77,099 and incremental quality-adjusted life-years (QALYs) = 0.0433, incremental cost-utility ratio (ICUR) = $1,273,444 per QALY.
- Change odds ratio of adverse cardiac events to 1 (base case 0.92, CI 0.53 to 1.63), incremental cost = $87,976 and incremental QALYs = 0.3536, ICUR = $248,766 per QALY.
- Change odds ratio to 1 for all non-significant events (survival and cardiac events), incremental cost = $77,184 and incremental QALYs = 0.0432, ICUR = $1,283,729 per QALY.
- Short time horizon. To assess the timing of accrual of benefits and costs, shorter time horizons were explored. Note that in the reference case incremental QALY is 3.45.
    - One year: Incremental cost = $30,062 and incremental QALY = 0.0047; ICUR = $ 6,396,077
    - Three years: Incremental cost = $66,240 and incremental QALY = 0.0728; ICUR = $ 909,484
    - Five years: Incremental cost = $79,066 and incremental QALY = 0.1609; ICUR = $ 491,400.

Nintedanib versus pirfenidone

- The only available (indirect) evidence does not suggest that significant differences exist for efficacy and harms of nintedanib versus pirfenidone for most outcomes. If odds ratios for nintedanib and pirfenidone are equal for survival, exacerbations, loss of lung function, discontinuation, and serious cardiac events, the cost saving from nintedanib is $7,685 (saving from treatment $6,736 and from adverse events $949).
- Keeping the same odds ratio as above and excluding costs on skin disorder and gastrointestinal perforation, the cost saving from nintedanib is $6,451 (saving from treatment $6,732 but additional adverse event cost of $281).
- Keeping the same odds ratio as above and lowering the costs on skin disorder (from $1,806 to $116.6, which includes a dermatologist consultation [A025] and a repeat consultation [A026], based on the Ontario Schedule of Benefits [date not stated]), the cost saving from nintedanib is $6,356 (saving from treatment $6,737 but additional adverse event cost of $380).

Note: Cost minimization analysis is adopted for nintedanib versus pirfenidone, as the estimates from the NMA are mostly insignificant. After odds ratios are set to equal, there is minimal QALY difference (< 0.02, approximately seven days of perfect health) in the model because of the underlying adverse events (serious gastrointestinal events, skin disorders, and gastrointestinal perforation). CDR has decided to focus on the treatment and adverse event costs where the two drugs differ.

TABLE 15: SUMMARY OF CADTH COMMON DRUG REVIEW RESULTS (NINTEDANIB VERSUS PIRFENIDONE)

	PFN	NTB	Incremental
Scenario 1 (Same OR)			
Total Cost[a] ($)	139,958	132,273	–7,685
• Treatment cost ($)	92,378	85,642	–6,737
• Adverse event ($)	4,151	3,203	–949
• Liver panel test ($)	70	70	0
• Patient monitoring and O_2 use ($)	34,425	34,425	0
• Acute exacerbation costs ($)	5,843	5,843	0
• End-of-life costs ($)	3,091	3,091	0
Total QALYs	3.4387	3.4536	0.0149
Scenario 2 (Same OR, No Skin Disorder and GI Perforation)			
Total Cost ($)	138,444	131,993	–6,451
• Treatment cost ($)	92,318	85,586	–6,732
• Adverse event ($)	2,729	3,010	281
Total QALYs	3.4524	3.4513	–0.0011
Scenario 3 (Same OR, Lower Skin Disorder Cost)			
Total Cost ($)	138,629	132,273	–6,356
• Treatment cost ($)	92,378	85,642	–6,737
• Adverse event ($)	2,822	3,203	380
Total QALYs	3.4387	3.4536	0.0149

CDR = CADTH Common Drug Review; GI = gastrointestinal; NTB = nintedanib; OR = odds ratio; PFN = pirfenidone; QALY = quality-adjusted life-year.

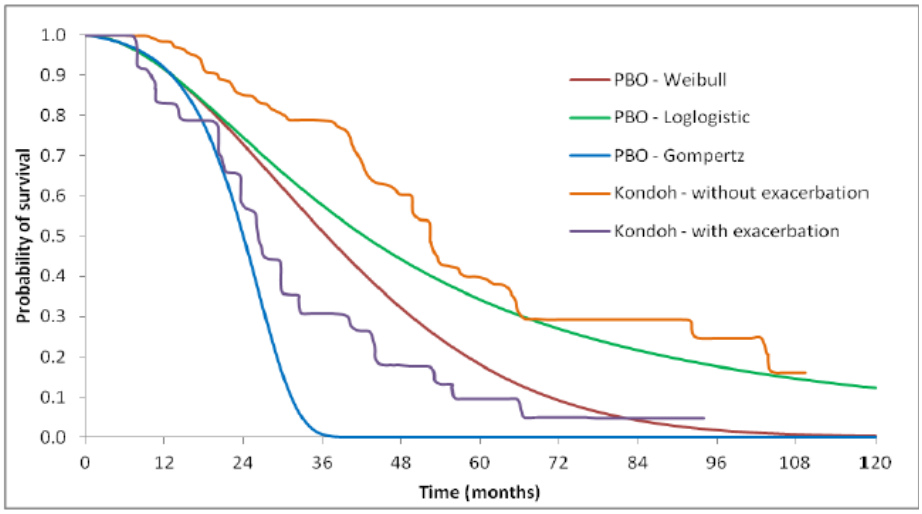
[a] For cost minimization analysis, only treatment costs and adverse event costs are different between the two drugs. Other costs stay the same as in Scenario 1.

Nintedanib versus N-acetylcysteine

- Change odds ratio on survival to 1 (as CI contains 1), best supportive care dominates.
- Change odds ratio on exacerbation to 1 (as CI contains 1), ICUR = $1,996 per QALY.
- Change odds ratio on serious cardiac events to 1 (as CI contains 1), ICUR = $2,051 per QALY.

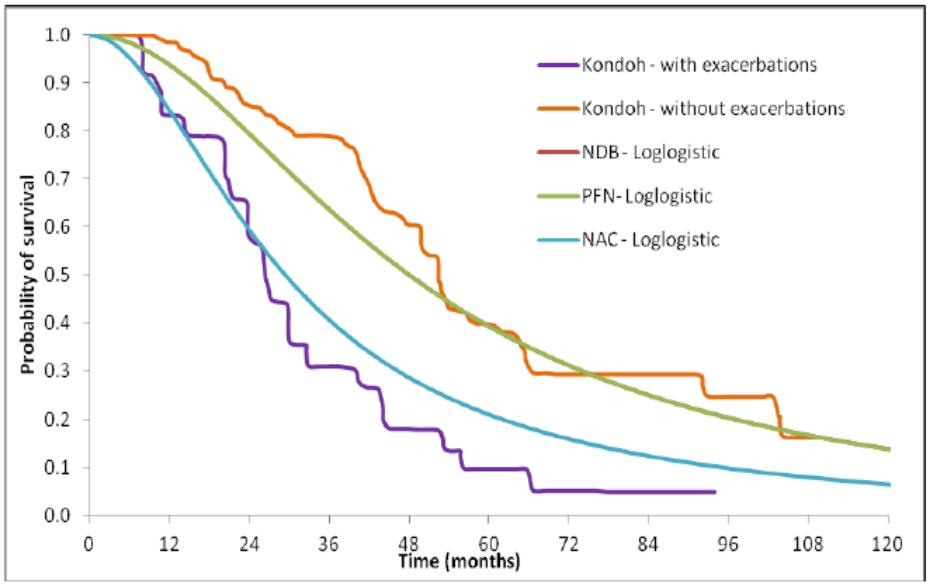
APPENDIX 5: FIGURES FROM MANUFACTURER'S SUBMISSION

FIGURE 2: OVERALL SURVIVAL EXTRAPOLATIONS FOR BEST SUPPORTIVE CARE GROUP



Source: Manufacturer's Pharmacoeconomic Submission,[3] page 26.
PBO - placebo

FIGURE 3: OVERALL SURVIVAL CURVE FIT



*Curves for NDB and PFN are overlapping

NAC = N-acetylcysteine; NDB = nintedanib; PFN = pirfenidone.
Source: Manufacturer's pharmacoeconomic submission,[3] page 28.

REFERENCES

1. [Pr]Ofev[TM] (nintedanib capsules): 100 mg and 150 mg nintedanib (as nintedanib esilate) [product monograph]. Burlington (ON): Boehringer Ingelheim (Canada) Ltd.; 2015 Jun 24.
2. CDR submission: Ofev[TM] (nintedanib), 100 mg and 150 mg capsules. Company: Boehringer Ingelheim (Canada) Ltd. [**CONFIDENTIAL** manufacturer's submission]. Burlington (ON): Boehringer Ingelheim (Canada) Ltd.; 2015 Apr 23.
3. Pharmacoeconomic evaluation. In: CDR submission: Ofev[TM] (nintedanib), 100 mg and 150 mg capsules. Company: Boehringer Ingelheim (Canada) Ltd. [**CONFIDENTIAL** manufacturer's submission]. Burlington (ON): Boehringer Ingelheim (Canada) Ltd.; 2015 Apr 23.
4. Clinical Study Report: 1199.32 [INPULSIS-1]. A 52 weeks, double blind, randomized, placebo-controlled trial evaluating the effect of oral BIBF 1120, 150 mg twice daily, on annual forced vital capacity decline, in patients with idiopathic pulmonary fibrosis (IPF) [**CONFIDENTIAL** internal manufacturer's report]. [Ingelheim am Rhein]: Boehringer Ingelheim International GmbH; 2014 Apr 8.
5. Clinical Study Report: 1199.34 [INPULSIS-2]. A 52 weeks, double blind, randomized, placebo-controlled trial evaluating the effect of oral BIBF 1120, 150 mg twice daily, on annual forced vital capacity decline, in patients with idiopathic pulmonary fibrosis (IPF) [**CONFIDENTIAL** internal manufacturer's report]. [Ingelheim am Rhein]: Boehringer Ingelheim International GmbH; 2014 Apr 8.
6. Clinical Study Report: 1199.30 [TOMORROW]. A 52 week, double blind, randomized, placebo-controlled trial evaluating the effect of BIBF 1120 administered at oral doses of 50 mg qd, 50 mg bid, 100 mg bid and 150 mg bid on forced vital capacity decline during one year, in patients with idiopathic pulmonary fibrosis, with optional active treatment extension until last patient out [**CONFIDENTIAL** internal manufacturer's report]. [Ingelheim am Rhein]: Boehringer Ingelheim International GmbH; 2011 Feb 25.
7. U.S. Food and Drug Administration. Highlights of prescribing information: Ofev® (nintedanib) capsules, for oral use [label] [Internet]. Rockville (MD): FDA; 2014 Oct. [cited 2015 May 15]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205832s000lbl.pdf
8. Cooper K, Mendes D, Picot J, Loveman E. Pirfenidone for treating idiopathic pulmonary fibrosis: a single technology appraisal. [Internet]. Southampton (UK): Southampton Health Technology Assessments Centre (SHTAC); 2012 Sep. [cited 2015 May 15]. (Evidence review group report commissioned by the NHS R&D HTA Programme on behalf of NICE). Available from: http://www.nice.org.uk/guidance/ta282/documents/idiopathic-pulmonary-fibrosis-pirfenidone-evidence-review-group-report2
9. Ara R, Brazier JE. Using health state utility values from the general population to approximate baselines in decision analytic models when condition-specific data are not available. Value Health. 2011 Jun;14(4):539-45.
10. Ontario Ministry of Health and Long-Term Care. Exceptional access program (EAP): formulary [Internet]. Toronto: The Ministry; 2015. [cited 2015 May 15]. Available from: http://www.health.gov.on.ca/en/pro/programs/drugs/odbf/odbf_except_access.aspx
11. Régie de l'assurance maladie du Québec (RAMQ). List of medications [Internet]. Quebec (QC): RAMQ; 2015. [cited 2015 May 15]. Available from: http://www.ramq.gouv.qc.ca/en/regie/legal-publications/Pages/list-medications.aspx
12. Kondoh Y, Taniguchi H, Katsuta T, Kataoka K, Kimura T, Nishiyama O, et al. Risk factors of acute exacerbation of idiopathic pulmonary fibrosis. Sarcoidosis Vasc Diffuse Lung Dis. 2010 Jul;27(2):103-10.