

**VALUE-BASED REAL OPTION ANALYSIS TO SUPPORT EARLY-STAGE DRUG
DEVELOPMENT**

by

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The following individuals certify that they have read, and recommend to the Faculty of Graduate and Postdoctoral Studies for acceptance, a thesis entitled:

VALUE-BASED REAL OPTION ANALYSIS TO SUPPORT EARLY-STAGE DRUG
DEVELOPMENT

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the degree of Master of Science
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ABSTRACT

Background: Value-based frameworks link costs with health outcomes and are considered in drug reimbursement, suggesting the increasing need to estimate commercial performance of novel drugs in relation to demonstrating cost-effectiveness.

Objective: To develop a value-based drug development framework and evaluate a commercialization strategy for a phase 1 drug candidate for hypoglycemia in type 1 diabetes (T1D).

Methods: A value-based real options analysis (VB-ROA) framework was developed to incorporate payer and for-profit investor perspectives by integrating cost-effectiveness analysis (CEA) with real options analysis (ROA). The framework was applied to commercially evaluate a phase 1 drug candidate to prevent hypoglycemia.

The VB-ROA framework was constructed in two stages:

1. Value-based price was estimated using headroom analysis based a Markov model assuming a US payers' willingness to pay (WTP, λ) of \$50,000 per quality-adjusted life year (QALY) and payers' discount rate (r_d) of 3%. The drug candidate's target product profile (TPP) was based on clinician reports on meaningful health improvements.
2. ROA via the binomial lattice option pricing model (BOPM) using revenues based on value-based pricing and a cost of capital (r_c) of 13.2%.

Data to populate model parameters were gathered from published clinical, regulatory, and market data.

Results: The value-based drug price was \$5,178 (95% CI \$4,437, \$5,956) per year per patient. The phase 1 development option value was \$0 ($V_{0,1}$). The development strategy could be abandoned or revised, which may involve partnering non-profit institutions. If successful, the development option for phase 2 is \$67 Million ($V_{1,1}$) or \$0 ($V_{1,2}$). If development leads to regulatory approval, the option value to launch ranges from \$8,716 Million ($V_{7,1}$) to \$127 Million ($V_{7,8}$). Sensitive parameters to option value include

investors' cost of capital (r_c), drug price, development risks (θ_t), market share, λ , health-related quality of life (HRQoL) weights, and the relative risk of non-severe hypoglycemia (RR_{NSHday} & RR_{NSHnoc}).

Conclusions: The VB-ROA framework aligns patient, payer, and investor incentives to assess the impact of clinical and cost-effectiveness parameters on the commercial potential of novel drugs, which further enables the development novel drugs that are affordable for payers and patients, while profitable for investors.

LAY SUMMARY

Healthcare costs are rising due to high drug prices. There is increasing pressure from payers (e.g., private insurers) to set drug prices based on health benefits experienced by patients. Commercialization strategies for early-stage drug candidates did not adequately consider payer needs. To develop affordable products, a value-based drug development framework that combines the needs of corporate investors and payers was made by assessing a drug's commercial potential using revenues based on prices that align with its health benefits. This framework was used to evaluate a drug candidate for hypoglycemia. Results suggest it is unlikely to be an attractive for-profit investment with its current development strategy. The strategy could be revised for improved performance (i.e., patient outcomes and cost-savings), or financing sourced from non-profit partnerships. This framework also serves as a tool to collaborate between the pharmaceutical industry and payers in effective reimbursement discussions.

PREFACE

With the guidance of my thesis committee advisors, I was responsible for the analyses presented in Chapter 3 (headroom analysis) and Chapter 4 (real option analysis). The headroom analysis to estimate the value-based price of a drug to prevent hypoglycemia was performed by myself with the support of Dr Dean Regier and Dr. Richard Liggins. I conducted the real options analysis to estimate the commercial value of the drug candidate with the support of Dr. Ron Giammarino.

TABLE OF CONTENTS

Abstract.....	iii
Lay Summary.....	v
Preface	vi
Table of Contents.....	vii
List of Tables	x
List of Figures	xi
List of Equations	xii
List of Abbreviations	xiii
Acknowledgements.....	xv
Chapter 1. Introduction.....	1
1.1 Challenges in healthcare.....	1
1.2 Declining productivity and profitability in drug development	3
1.3 Value-based healthcare.....	5
1.4 Collaborative healthcare decision-making	7
1.5 Objective and aims	7
Chapter 2. VB-ROA Framework Development	9
2.1 Cost-effectiveness analysis (payer perspective).....	9
2.2 Drug development	14
2.3 Value-based pricing and headroom analysis	17
2.4 Real options analysis to support development decisions.....	19
2.4.1 Binomial option pricing model	22
2.5 Value-based real options analysis framework.....	28
Chapter 3. Value-based price for an early-stage drug that prevents hypoglycemia	33
3.1 Study Objective	33
3.2 Introduction	33

3.2.1	Clinical background	33
3.2.2	Somatostatin receptors and hypoglycemia.....	36
3.3	Methods.....	37
3.3.1	Target product profile	38
3.3.2	Model structure	39
3.3.3	Clinical parameters	42
3.3.4	Cost parameters.....	45
3.3.5	Sensitivity analysis.....	47
3.4	Results	50
3.4.1	Value-based price of an SSTR2a drug that prevents hypoglycemia.....	52
3.4.2	One-way sensitivity analysis.....	55
3.4.3	Scenario analysis.....	56
3.5	Discussion	58
3.5.1	Limitations	60
Chapter 4.	VB-ROA of a Phase 1 Drug Candidate.....	64
4.1	Introduction	64
4.2	Study Objective	65
4.3	Methods.....	65
4.3.1	Market value of the SSTR2a drug candidate	66
4.3.2	Calculating option value	69
4.3.3	Sensitivity analysis.....	70
4.4	Results	71
4.4.1	Base case	71
4.4.2	One-way sensitivity analysis.....	74
4.5	Discussion	77
4.5.1	Limitations	79
Chapter 5.	Implications and Conclusions	81
5.1	Sensitivity analysis on VB-ROA to construct development strategies to ‘fail faster’	81
5.2	The need for risk-sharing drug development partnerships	82
5.3	Further applications of the VB-ROA framework.....	83
5.4	Limitations to the VB-ROA framework.....	83
5.5	Conclusions	84

References.....	86
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LIST OF TABLES

Table 1:	Target product profile for an SSTR2a drug candidate.....	39
Table 2:	Summary of clinical parameters inputted into the cost-effectiveness analysis.....	43
Table 3:	Direct healthcare costs for hypoglycemic events and insulin therapy.....	46
Table 4:	Patient cohort baseline characteristics.	50
Table 5:	Summary of simulated model inputs.....	51
Table 6:	Value-based price and headroom analysis results for the SSTR2a drug candidate.....	54
Table 7:	Point estimates for base case and scenario analysis of value-based price.	57
Table 8:	Breakdown of variables to calculate asset value.....	67
Table 9:	Summary of commercial parameter inputs for the binomial option pricing method.....	68
Table 10:	Binomial option pricing method input parameters for asset values ($A_{t,k}$).	69
Table 11:	Drug development parameters for BOPM.	70

LIST OF FIGURES

Figure 1:	Overall prescription price index.	2
Figure 2:	Overall trend in R&D efficiency (1950-2010, inflation adjusted).	3
Figure 3:	Frequency of drugs excluded from reimbursement by US payers.	4
Figure 4:	A taxonomy of value-based arrangements.	6
Figure 5:	Cost-effectiveness plane.	12
Figure 6:	Sample cost-effectiveness acceptability curve.	14
Figure 7:	Top global drug sales in 2017 and 2018.	16
Figure 8:	Drug development model from phase 1 to market launch.	17
Figure 9:	Comparing real option value (V) and risk-adjusted net present value (rNPV).	22
Figure 10:	Asset and option values in a binomial lattice.	24
Figure 11:	Overview of the value-based real option analysis (VB-ROA).	30
Figure 12:	Trends in diabetes prevalence (1980-2014) by country income category.	35
Figure 13:	Markov model schematic for the headroom analysis.	40
Figure 14:	Probability distribution of the annual value-based price.	53
Figure 15:	Tornado plot of one-way sensitivity analysis ($\pm 50\%$) on value-based price.	56
Figure 16:	Distribution in the market value of the drug candidate ($A_{t,k}$).	72
Figure 17:	Real option values ($V_{t,k}$) after adjusting for clinical development risks ($\theta_{t,k}$).	73
Figure 18:	One-way sensitivity analysis results on the VB-ROA	76

LIST OF EQUATIONS

Equation 1:	Quality-adjusted life year (QALY) calculations.....	10
Equation 2:	Incremental cost-effectiveness ratio (ICER).....	11
Equation 3:	Calculating Net monetary benefit from cost-effectiveness analysis.....	13
Equation 4:	Calculating the value-based price through headroom analysis.	18
Equation 5:	Free cash flow (FCF) calculation.....	19
Equation 6:	Formula for risk-adjusted net present value (rNPV).	19
Equation 7:	Binomial option pricing model algorithm.....	23
Equation 8:	Calculating the market value of the drug development project.	25
Equation 9:	Upward (u) and downward (p) asset price ($A_{t,k}$) adjustments using σ	26
Equation 10:	Example option value ($V_{7,1}$) calculation at a terminal decision node.	27
Equation 11:	Calculating options on future options (i.e., nested options).	27
Equation 12:	Calculating the risk-neutral probability	27

LIST OF ABBREVIATIONS

95% CI	95% confidence interval
BLA	Biologics license application
BOPM	Binomial option pricing model
CDN	Canadian dollar(s)
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CGM	Continuous glucose monitoring
COGS	Cost of goods sold
DCF	Discounted cash flow
EMA	European Medicines Agency
FCF	Free cash flow
FDA	US Foods and Drug Administration
G&A	General and administrative costs
GDP	Gross Domestic Product
HRQoL	Health-related quality of life
IAH	Impaired awareness of hypoglycemia
ICER	Incremental cost-effectiveness ratio
ISPOR	International Society for Pharmacoeconomics Outcomes Research
NDA	New drug application
NDA	New drug application
NICE	National Institute for Health and Care Excellence
NPV	Net present value
NSH	Non-severe hypoglycemia
OECD	Organisation for Economic Cooperation and Development
QALY	Quality-adjusted life year
R&D	Research and development
rNPV	Risk-adjusted net present value
RR	Relative risk

SH	Severe hypoglycemia
SMBG	Self-monitoring blood glucose
SSTR2a	Somatostatin receptor type 2 antagonist
TPP	Target product profile
UK	United Kingdom
USD	US dollar(s)
VBP	Value-based price
VB-ROA	Value-based real options analysis
WTP	Willingness to pay

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Lastly, the most valuable lesson that I have learned from all of you is that we grow more through fruitful relationships than the fruits of our individual labour.

CHAPTER 1. INTRODUCTION

The need to improve decision-making in the healthcare sector is explained in Chapter 1. This thesis builds upon research in the fields of drug development, finance, and health economics, which is described in Chapter 2. A value-based drug development decision framework combining headroom and real options analyses was developed through discussions with subject-matter experts in the fields of early-stage drug development (Dr. Richard Liggins), health economics (Dr. Dean Regier), and corporate finance (Dr. Ron Giammarino).

1.1 Challenges in healthcare

Healthcare systems are challenged to provide patients with access to quality medical care in a sustainable manner.^{1,2} 2017 healthcare spending for US and Canada, respectively, was \$3.5 trillion USD and \$253.5 billion CDN, making up 11.1% and 17.9% of its gross domestic product (GDP).^{3,4} Spending continues to increase in both OECD countries by approximately 4% annually from 2017 to 2018.^{3,4}

Increase in spending often does not translate to better access to care, nor better quality of care. In Canada, wait times have increased by 113% since 1993 to a median waiting time of 19.8 weeks.⁵ In the US, 28 million (MM) people remain uninsured and healthcare expenditures are projected to grow annually by 5.6% from 2016 to 2025 and eventually make up 20% of GDP.⁶ The increase in expenditures impacts patients through insurance premium increases. In 2017, 37% of US insured adults had difficulty affording premiums, and close to 14 million Americans failed to receive necessary medical care due to costs.⁶

In Canada, 70% (\$177.5 billion) of total health expenditure is covered through public-sector funding, with the remaining funded through private insurance or out-of-pocket payments.⁷ In the US, household health care spending (e.g., out-of-pocket, insurance premiums) constituted 28% (\$ 980 billion) of total health spending in 2017. Canadian hospital spending contributed to 28.3% (\$71.74 billion) of

total healthcare spending, whereas, drugs spending make up 15.7% (\$39.8 billion).⁷ US healthcare spending contributed 10% (\$333.4 billion) to retail drug prescriptions.⁴

Both Canada and the US experienced increases in spending for prescription drugs due to the higher cost of novel therapeutics and increased consumption.^{4,7,8} The pharmaceutical industry has been criticized for the high price for novel therapies.⁹ Overall branded prescription drug prices has increased by 62.1% from 2014 to 2018 (Figure 1). In comparison, generic drug prices decreased by 36.9% and cost of household goods rose by 7.4% within the same timeframe.⁸

Novel therapeutics developed for oncology and rare genetic diseases continue to increase in price to unaffordable levels. The cost of a year of life gained with cancer treatment has been increasing by \$8,500 per year as a result of increasing prices for oncology drugs.⁸ Gene-based therapies such as Strimvelis and Glybera have been priced at \$665 thousand and \$1 million USD per treatment.^{10,11} In fact, due to price, Glybera was voluntarily taken out of the market by UniQure a year after receiving regulatory approval.¹⁰

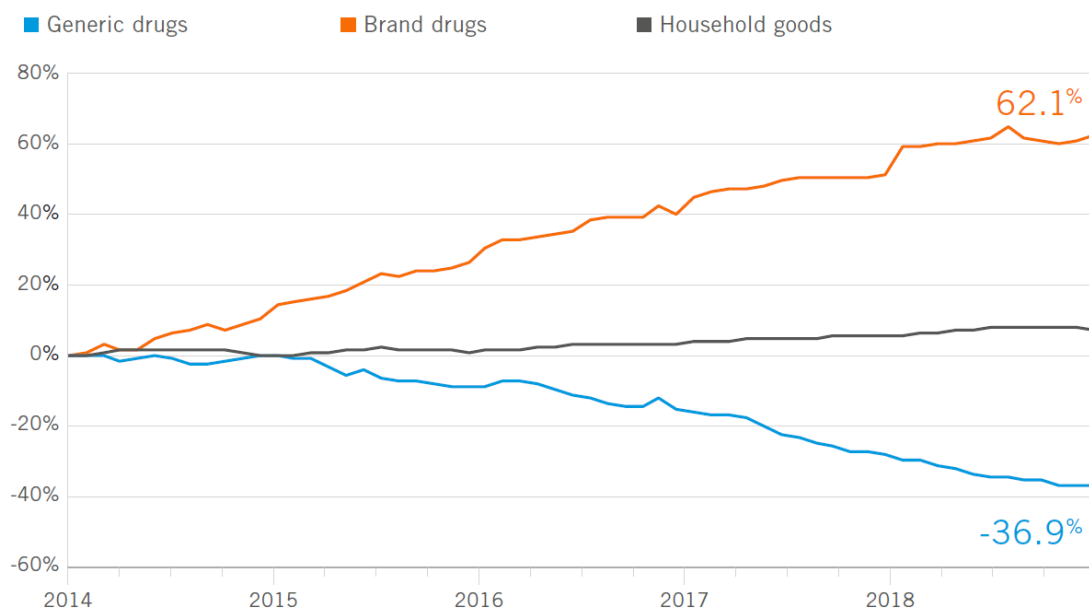


Figure 1: Overall prescription price index.Source: *Express Scripts (2018)*.⁸

1.2 Declining productivity and profitability in drug development

Even with high drug prices to increase profit margins, the return on investment is low and the pharmaceutical industry is struggling to be productive with their drug development resources. The number of newly approved drugs per billion US dollars spent on research and development (R&D) reduced by 50% every 9 years from 1950 – 2010 (Figure 2).¹² Development cost per novel drug increased to \$2 billion USD, while the output of novel therapies remain stagnant.^{13–15}

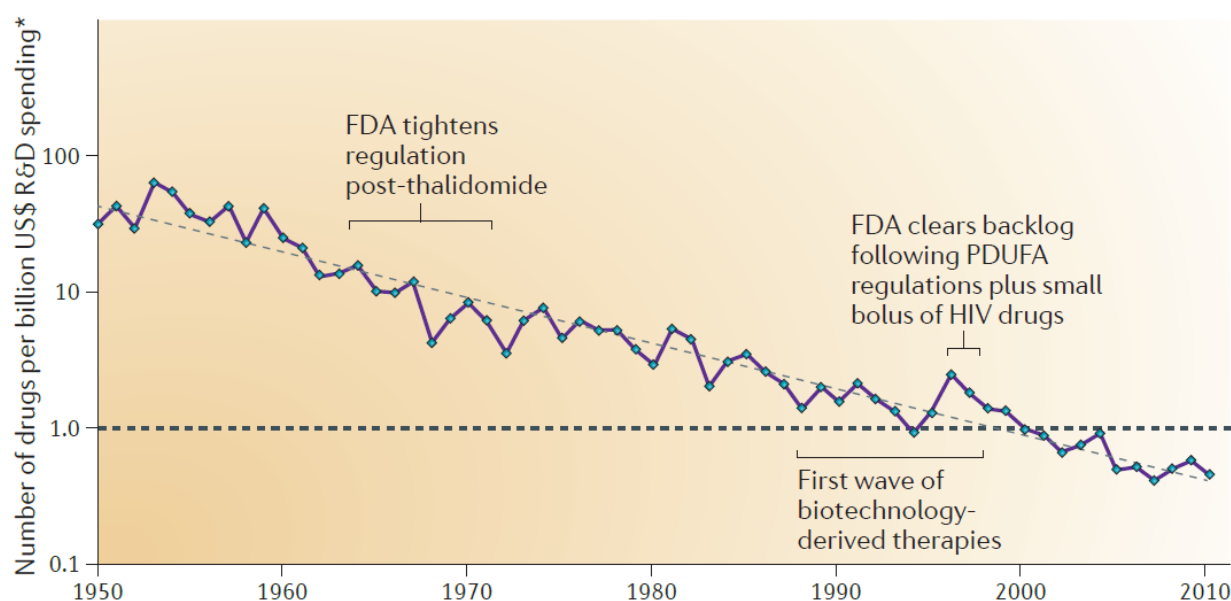


Figure 2: Overall trend in R&D efficiency (1950-2010, inflation adjusted).Source: Scannell et al (2012).¹²

It has been previously reported that up to 30% of drug candidates are abandoned after health economic assessments.^{16,17} Recent industry performance has been poor where only 34% of newly approved drugs met or exceeded its sales expectations¹⁸, which resulted in an estimated investment return of 3.7%.¹⁹ Revenue projections of newly approved therapies tend to be exaggerated, where 43% of forecasts were overestimated by 40%.^{20,21}

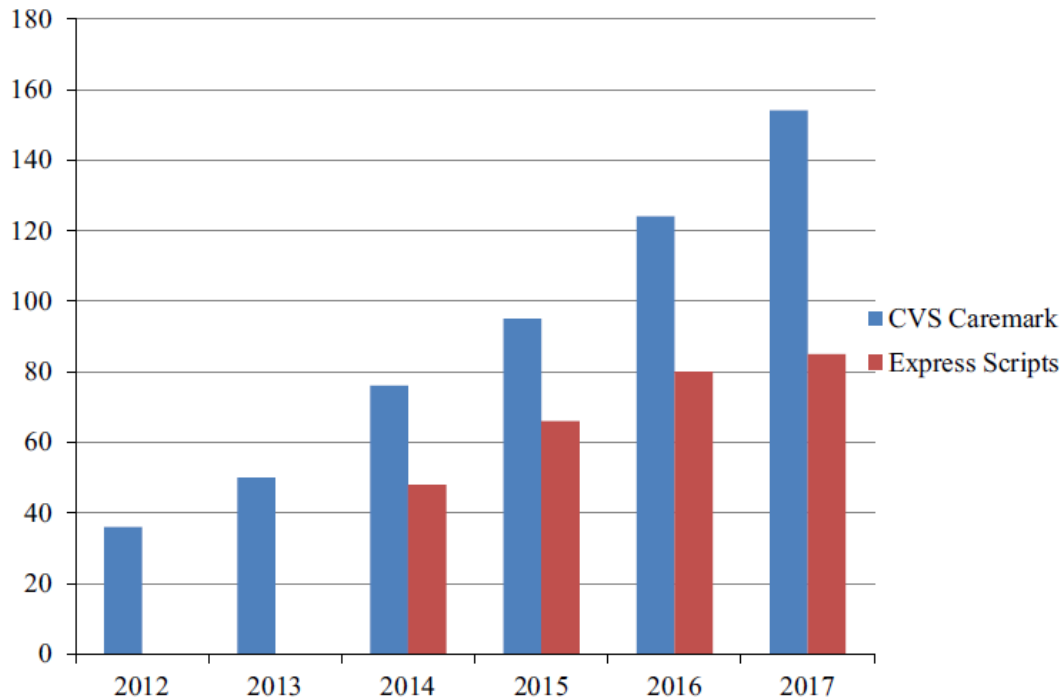


Figure 3: Frequency of drugs excluded from reimbursement by US payers. CVS Caremark and Express Scripts are the two largest pharmacy benefit managers in the US. Source: Cohen et al., 2017.²²

There could be many reasons attributed to the low productivity in R&D spending. Attributable factors include: changes in regulatory landscape, increase in clinical trial costs and timelines, as well as higher reimbursement requirements for cost-effectiveness.¹⁴ Although drug companies have pricing power due to patent rights, there is increasing pressure from payers to lower prices as they struggle to contain rising healthcare costs. From 1998 to 2008, the UK's National Institute for Health and Care Excellence (NICE) granted restricted or no market access to approximately 60% of approved drugs from the top ten pharmaceutical companies.²³

Payer requirements have the potential to increasingly influence profitability of drug products. An empirical study shows that 239 drug products were in the excluded from drug formularies provided by two of the largest US-based pharmacy benefit managers (Figure 3).²²

1.3 Value-based healthcare

One possible contribution to the increase in reimbursement delays and rejections is the increasing adoption of value-based healthcare.² Value-based healthcare aims to maximize the value extracted through healthcare spending in terms of patient outcomes at a population level. In an effort to contain healthcare costs, both public and private payers are increasingly embracing value-based reimbursement strategies such as performance-based risk sharing arrangements, especially for oncology and diabetes treatments.^{1,24–26} These payment models involve agreements where reimbursement levels (i.e. price) correspond to drug performance at improving health and economic outcomes in a defined patient population.^{27,28}

According to the ISPOR Performance-Based Risk Sharing Arrangements Good Practices Task Force (2013)²⁸, value-based reimbursement agreements have the following key characteristics:

1. Post-approval data collection agreements between payers and manufacturers on patient outcomes that underlie reimbursement structure.
2. Data collection (e.g., post-approval real world studies) is intended to address uncertainty in a drug's cost-effectiveness pertaining to the target population compared with usual care.
3. Price, level of reimbursement, and product revenue are linked to patient health outcomes via options to renegotiate coverage, or individual performance guarantees, etc.

Value-based reimbursement agreements can be segmented into those that aim to 1) better manage utilization in the real world and 2) to provide coverage with evidence development ([Figure 4](#))^{27,28}. The former aims to link drug performance and reimbursement at the individual patient level through “outcome guarantees” (i.e., payment for responders only), “conditional treatment continuation” (i.e., payments of conditional use subject to change based on clinical end points), and money back guarantees. The latter

aims to provide drug coverage while evidence on clinical and economic value is further developed either while patients participate in clinical trials or broader coverage conditional on additional data collection (post-approval surveillance).

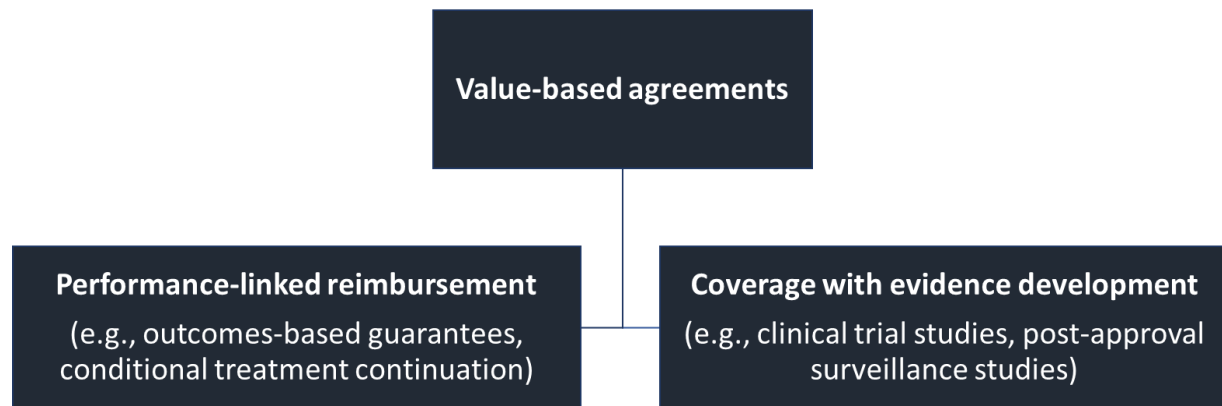


Figure 4: A taxonomy of value-based arrangements.²⁸

There have always been uncertainties regarding the economic and clinical performance of new drugs. Payers bear the risk of a product that performs poorly, whereas drug development firms bear the commercial risks of R&D investments.²⁹ Value-based reimbursement contracts benefits payers by reducing financial risks associated with uncertainty in drug performance.²⁸ Such agreements enable pharmaceutical firms to better estimate future revenues using evidence on clinical efficacy. This suggests that the profitability of novel drugs will increasingly be tied to the drug's cost-effectiveness at improving patient health outcomes. Therefore, it will be increasingly important to incorporate payer perspectives throughout the development process when making decisions to invest in the R&D of novel therapies.^{23,26,30}

Incorporating payer perspectives throughout the drug development process requires the adoption of a value-based framework at the beginning stages of development. Headroom analysis is a method that aims to support development decisions while considering reimbursement by calculating the monetary value that the new treatment can command based on payers' requirements for 'value-for-money'. The

calculated headroom has been proposed as an indicator for a drug's potential commercial success in context to reimbursement.³¹

1.4 Collaborative healthcare decision-making

The US has implemented value-based payment schemes for select Medicare plans since 2010^{25,32} with mixed or inconclusive results^{1,25,28,32}. Although value-based reimbursement has the potential to transform healthcare delivery and improve its performance, there are key challenges centered on a lack of cooperation across payers and drug manufacturers.^{25,28,32–34} Common issues underlying the lack of collaboration can be summarized as follows^{33,34}:

1. *Lack of digital infrastructure* to measure and collected outcomes data.
2. *Misaligned stakeholder values* including agreeing on outcome measures and the incentives needed to offset the cost of implementing value-based agreements.
3. *Lack of trust and accountability* between payers and drug manufacturers.

To advance healthcare quality through innovative technologies, stakeholders across the healthcare sector need to take collaborative approaches to develop and implement them. What is lacking to facilitate this effort is a framework that captures the perspective and needs of each stakeholder group. Private-public partnerships have emerged in translational research to improve early-stage R&D productivity, especially in under-served markets^{35–37}. Similar partnership models between payers and drug manufacturers that enable shared decision-making earlier in the development process can better enable value-based healthcare delivery.

1.5 Objective and aims

The objective of my thesis is to develop a value-based drug development decision framework to enable the development of cost-effective therapies by integrating the perspectives of payer and industry decision-makers. A value-based real options analysis (VB-ROA) framework was developed by

integrating cost-effectiveness (payer perspective) and real options analysis (industry perspective), which was applied to evaluate an early-stage drug development decision for a phase 1 drug candidate. This research was approached with the following specific aims:

1. Develop a value-based drug development decision framework informed through literature on health economic evaluation supporting payer reimbursement; and drug development (investment) decisions. [[Chapter 2](#)]
2. Calculate the value-based price of an early-stage (phase 1) drug candidate that prevents hypoglycemia for a US type 1 diabetes population through cost-effectiveness analysis (headroom method). [[Chapter 3](#)]
3. Value the option for a drug manufacturer to develop the SSTR2a drug candidate by inputting the value-based price into a binomial option pricing model informed through published evidence. [[Chapter 4](#)]

We begin by describing the development of the VB-ROA framework and proceed to apply the framework to analyze the decision to finance the development of a phase 1 drug candidate aimed at preventing hypoglycemia for type 1 diabetes (T1D) patients in the US.

CHAPTER 2. VB-ROA FRAMEWORK DEVELOPMENT

A value-based real options analysis (VB-ROA) framework was developed through a review of published literature on major health economic and financial valuation models, which identified that payers use cost-effectiveness analysis to inform reimbursement decisions^{25,28} and drug development decisions are informed through financial valuation models^{30,38–41}. The VB-ROA was constructed by nesting a cost-effectiveness model within real options analysis by using a value-based price (VBP) to estimate the financial benefits of a drug development project ([Figure 11](#)). The analysis was performed through the perspective of US-based payers and for-profit investors (incl. drug manufacturers). The following overview of the theoretical concepts underlying the VB-ROA framework is provided below:

- Cost-effectiveness analysis ([Section 2.1](#)),
- Drug development process ([Section 2.2](#)),
- Headroom analysis for value-based pricing ([Section 2.3](#)),
- Real options analysis to support development decisions ([Section 2.4](#)).

[Section 2.5](#) describes the VB-ROA framework in detail and how it is constructed to support development decisions on early-stage technologies.

2.1 Cost-effectiveness analysis (payer perspective)

Private (e.g., pharmacy benefit managers) and public (e.g., healthcare systems) payers reimburse health services and products (e.g., drug therapies) on behalf of the population under their care. Reimbursement agreements between payers and drug manufacturers involve negotiations on drug prices and corresponding payment terms. When making these arrangements, payers apply cost-effectiveness analysis (CEA)^{25,28,29}. CEA compares the costs associated with providing patients access to treatment against the health benefits it provides.

Health benefits can be measured in different ways, but typically considers life years gained in terms of quantity and quality. The quality-adjusted life year (QALY) is a health outcome measure that combines the number of life years gained with the quality of those life years (Equation 1). Quality of life is incorporated into the QALY by adjusting the number of life-years gained with health-related quality of life (HRQoL) weights. HRQoL weights are typically anchored on 0 and 1, where 0 is death and 1 is perfect health.⁴² The QALY has been widely applied in health technology assessments, which allows treatments from different disease indication to be easily compared.⁴² Other outcome measures (e.g., adverse events forgone) can be applied depending on payer preferences and jurisdiction-specific priority setting processes.⁴³

$$QALY = [HRQoL] \times [\# \text{ of life years gained}]$$

Equation 1: Quality-adjusted life year (QALY) calculations by adjusting the gain in life years with health-related quality of life (HRQoL) weights.

CEA modeling requires data on health outcomes, survival, disease epidemiology, resource use, costs, and patient quality-of-life measurements.⁴³ The model calculates the incremental cost (ΔCost) of gaining an incremental QALY (ΔQALY) when using a drug product to treat a population of patients that would benefit from it^{42,43}. To solve for these incremental values, CEA compares two (or more) treatment pathways where the target population receives either new treatment(s) or usual care. Within each treatment pathway, CEA projects patient outcomes gained, and healthcare expenditures incurred by the target population over a defined time horizon to calculate total costs and QALYs. Future costs and health benefits are discounted into present value terms using the payers' discount rate (r_d). The ΔCost and ΔQALY are calculated by subtracting the total costs ($\text{Cost}_{\text{new treatment}}$) and QALYs ($\text{QALY}_{\text{new treatment}}$) of the population receiving new treatment from the total costs ($\text{Cost}_{\text{usual care}}$) and QALYs ($\text{QALY}_{\text{usual care}}$) of the population receiving usual care (Equation 2).^{42–44}

$$\frac{Cost_{new\ treatment} - Cost_{usual\ care}}{QALY_{new\ treatment} - QALY_{usual\ care}} = \frac{\Delta Cost}{\Delta QALY} = ICER$$

$$ICER < \lambda$$

Equation 2: Incremental cost-effectiveness ratio (ICER) and its application to inform reimbursement decision based on payers' WTP (λ).

The incremental cost-effectiveness ratio (ICER) combines $\Delta Cost$ (numerator) with $\Delta QALY$ (denominator) to a single measure that is used to assess if a drug product is providing payers adequate 'value-for money' (Equation 2). From an economic perspective, value relates to what people are willing to pay.⁴⁵ For drug reimbursement, the value of a healthcare technology corresponds to payers' willingness to pay (λ , WTP) for an incremental gain in population health ($\Delta QALY$). Payers' λ varies across disease indications and countries. In the UK, NICE has published a range of acceptable λ values between \$26,000 to \$40,000 USD (20,000 € to 30,000 €).⁴⁶ In the US, λ has been cited as typically between \$50,000 to \$150,000 USD per QALY [1 to 3 times national gross domestic product (GDP) per capita] as per World Health Organization's (WHO) recommendations.^{47,48}

Estimated ICERs need to be less than λ for payers to reimburse a new drug therapy (Equation 2), but a single estimate does not mean the drug will always generate a cost-effective outcome. There is uncertainty in the information used to populate the cost-effectiveness model, therefore, there is uncertainty in the reimbursement decision. In order to evaluate the level of uncertainty in the ICER estimate, simulation techniques can be applied to generate a distribution of ICER estimates.

The simulated ICER estimates can be plotted on a cost-effectiveness plane to assess cost-effectiveness under uncertainty (Figure 5). The cost-effectiveness plane is a graphical representation of cost-effectiveness, where the horizontal and vertical axis represents the $\Delta QALY$ and $\Delta Cost$, respectively. There are four quadrants that make up the cost-effectiveness plane that have different indications for cost-effectiveness (Figure 5). ICER estimates that are plotted in quadrants 1 and 3 are negative, whereas quadrants 2 and 4 are positive. It is important to note that negative ICER estimates do not imply cost-

effectiveness. Negative ICER estimates can be attributed to negative ΔCosts or ΔQALYs (see Quadrant 1 and 3 of Figure 5).

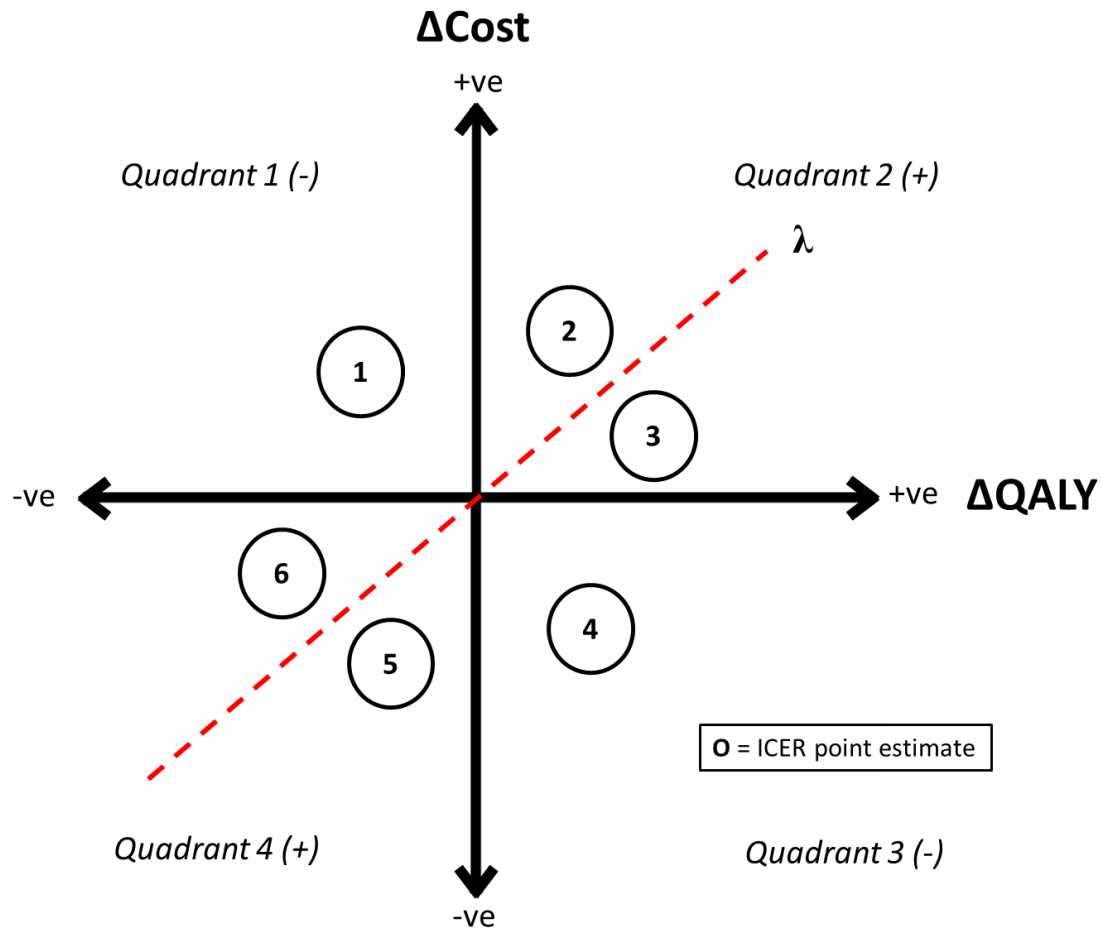


Figure 5: Cost-effectiveness plane. ΔQALY : incremental quality-adjusted life years, ΔCost : incremental costs, λ : payers' willingness to pay for incremental QALY. Quadrants 1 and 3 contain negative ICERs and quadrants 2 and 4 have positive ICERs. ICER point estimates 3, 4, and 5 are cost-effective ($<\lambda$), where as ICERs 1, 2, and 6 are not cost-effective ($>\lambda$).

The λ is represented through the slope (red dotted line) where ICERs below the slope are considered cost-effective and ICERs above are considered not cost-effective. The proportion of ICER estimates that lie below λ corresponds to the probability of the new treatment being cost-effective based on the payers' WTP.

Cost-effectiveness can also be expressed as incremental net monetary benefit, which converts the health benefit of the ICER into a single monetary value (Equation 3). An incremental cost that is negative implies that the new treatment has a cost-saving effect. The monetary value of the incremental gain in health benefit is determined by λ . A positive net monetary benefit (NMB) implies that the new treatment adds a net positive return and is considered cost-effective. A negative NMB implies the new treatment is not cost-effective.

$$\text{NMB} = \Delta\text{QALY} \times \lambda - \Delta\text{Cost}$$

Equation 3: Calculating Net monetary benefit from cost-effectiveness analysis. NMB: net monetary benefit, ΔQALY : incremental quality-adjusted life years, ΔCost : incremental costs, λ : payers' willingness to pay for incremental QALY.

The net monetary benefit can be calculated for each simulated ΔCosts and ΔQALYs using a range of λ thresholds to evaluate the uncertainty of the new treatment being cost-effective over usual care. This graphical representation of uncertainty of the CEA is referred to as the cost-effectiveness acceptability curve (CEAC) and is shown in Figure 6. As the payers' WTP threshold increases in value, the probability of the new treatment being cost-effective increases.

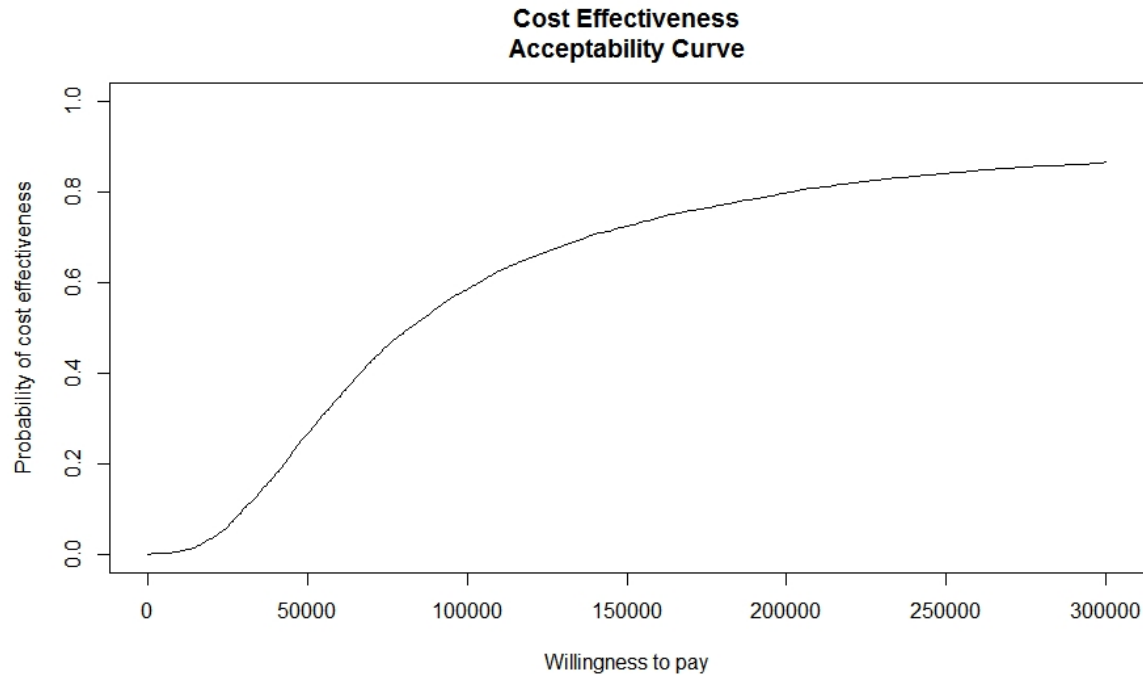


Figure 6: Sample cost-effectiveness acceptability curve. λ : Payers' willingness to pay threshold for a QALY.

Reimbursement decisions assume budgetary constraints exist for payers where financing one drug therapy will require spending less on other therapies. As such, λ reflects the payers' opportunity cost of displacing funds for one treatment program to reimburse another⁴². The capital budget to reimburse healthcare services is funded through taxes (public healthcare) and insurance premiums (private healthcare) collected from the population that is under the payers' care. Given that these budgets are limited, funds need to be rationed across a range of disease indications and distributed across the medical needs of the entire population. Therefore, reimbursement decisions coming from a payer perspective not only consider cost-effectiveness but also budgetary constraints.

2.2 Drug development

The drug development process can be viewed as a series of stage-gates with binary outcomes (go/no go), where each successive stage in development depends on the likelihood of passing through the gate at the previous stage (Figure 8).^{16,38} Drug development begins with preclinical research to discover

promising drug candidates followed by three successive clinical trials to assess their safety and efficacy. Decision-makers review evidence generated from respective R&D studies to support their go/no go decisions throughout the development process. Regulatory authorities (e.g., FDA, Health Canada, European Medicines Agency) review the scientific evidence generated from preclinical and clinical studies for market approval decisions. Upon regulatory approval, further cost-effectiveness evidence is required to support reimbursement of the final product.

Drug development projects are characterized by long investment time frames, low probabilities of success, and high costs. The probability of successfully bringing an early-stage drug candidate to market is 4-7%, where the underlying reasons for attrition are due to lack of efficacy (56%), safety (28%), changing strategies (7%), commercial reasons (5%), and operational challenges (5%).¹⁵ Bringing a preclinical drug to market can take 10 years to complete and can cost from \$1.4 to \$2.9 billion USD.^{13,15} Patent rights for novel technologies function to reward investors for bearing the risks with drug development, and annual sales of successful drugs can reach up to \$20 billion USD ([Figure 7](#)).⁴⁹⁻⁵¹

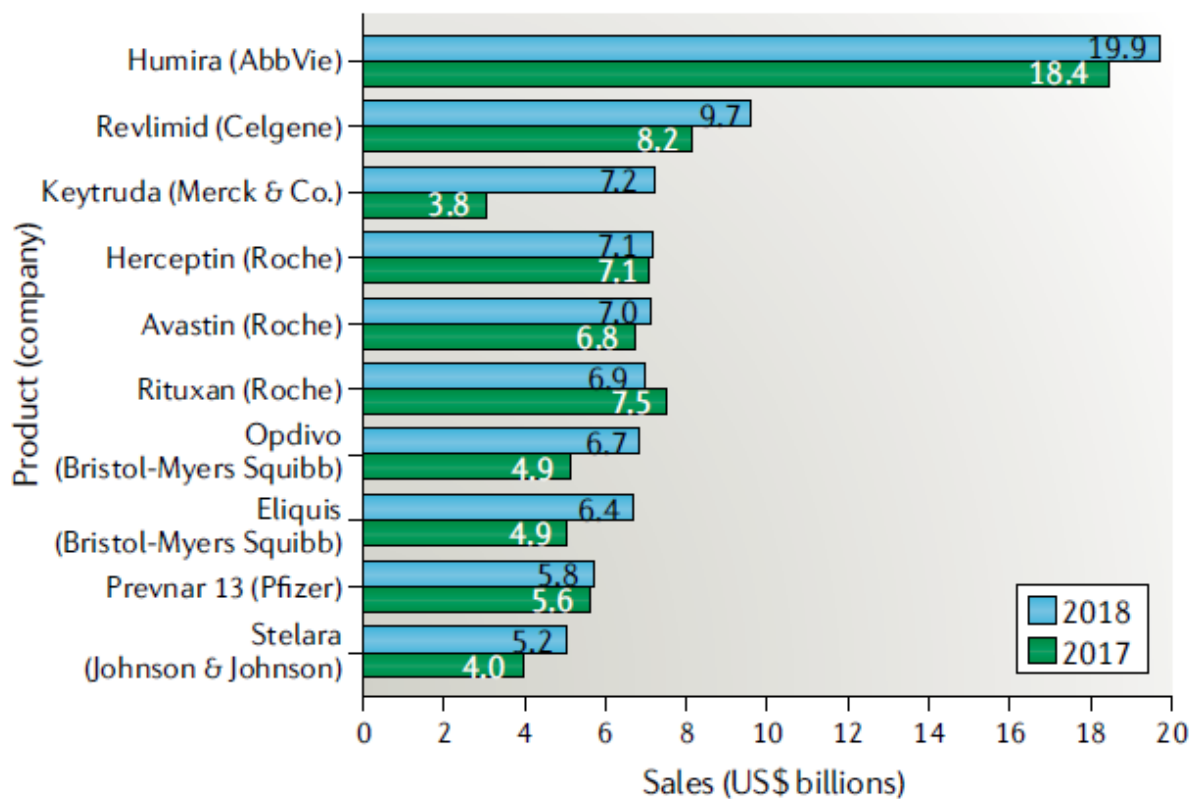


Figure 7: Top global drug sales in 2017 and 2018.Source: *Urquhart, 2019*.⁵⁰

There are commercial (e.g., market size, growth) and technical risks in drug development.^{16,38}

Technical risks are associated with regulatory approval, which require drug companies to demonstrate the safety & efficacy of the drug in development. Technical uncertainties are de-risked as the drug candidate progresses through clinical trials. Phase 1 studies evaluate the safety profile of the drug, and phase 2 and 3 studies assess clinical efficacy.^{16,38}

Time (t)	Yr 0	Yr 1	Yr 3	Yr 6	Yr 7
Capital Expenditures (\$MM, 2018), S_t	\$27.93	\$64.70	\$281.98	\$2.40	\$94.30
Probability of Phase Success, θ_t	63%	29%	56%	73%	100%

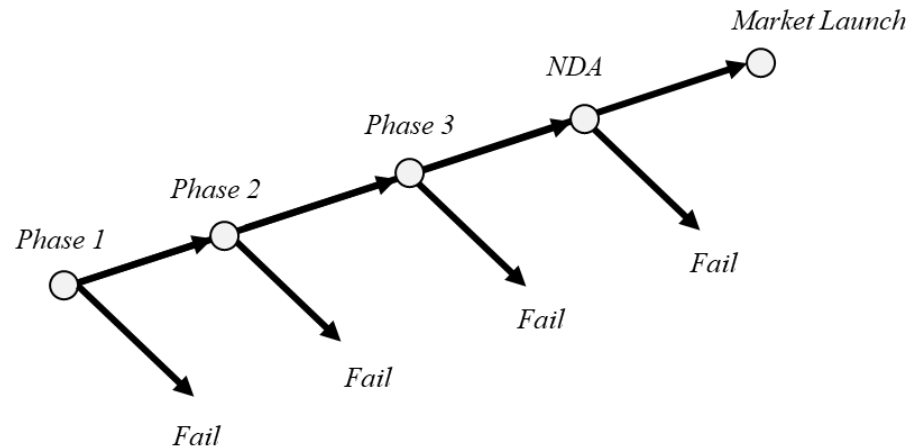


Figure 8: Drug development model from phase 1 to market launch. S_t : cost to finance development phase, θ_t : probability of successfully passing development phase. Costs¹³, length of trials⁵² and probabilities of success⁵³ were taken from published literature.

Commercial risks are associated with market factors that influence profits including competitor threats, market size, growth rate, and pricing. Much of the mentioned commercial uncertainties are sensitive to the reimbursement status of the drug product. Drug reimbursement status can include the following: 1) adopt, 2) adopt with performance-based agreement, 3) adopt with further evidence 4) decline and seek further evidence.⁵⁴ A drug's reimbursement status will likely impact a drug manufacturer's revenue (e.g., market size) and costs (e.g., to fund post-approval studies). Therefore, payer requirements should be considered when estimating commercial value.

2.3 Value-based pricing and headroom analysis

The value-based price (VBP) is the maximum price a drug manufacturer can charge payers while meeting their cost-effectiveness requirements, which can be estimated through headroom analysis. Headroom analysis is a form of cost-effectiveness analysis (CEA) that estimates the maximum price that

can be charged in which the treatment will be cost-effective for payers based on their willingness to pay (i.e., λ) for health outcomes.³⁹

Headroom analysis is an extension of cost-effectiveness analysis to support drug development decisions.^{31,55} It is a method that quantifies the potential of a new technology at improving current clinical practice in terms of health outcomes and costs.^{39,56} Headroom analysis considers λ , the effectiveness gap ($\Delta QALY = QALY_{\text{new treatment}} - QALY_{\text{usual care}}$), and net additional costs or savings ($\Delta Cost^{\#} = \Delta Cost_{\text{new treatment}} - \Delta Cost_{\text{usual care}}$) from using the new treatment compared to usual care. The effectiveness gap is the increase in the effectiveness of a new technology compared to the reference standard (e.g., usual care).

Importantly, the cost of purchasing the new treatment (i.e., new drug price) is not considered in headroom analysis.^{31,39,56,56} By doing so, the calculated net monetary benefit (i.e., headroom) reflects payers' views on the value of the new treatment due to downstream improvements in health outcomes and changes in healthcare costs compared with usual care. If price of the new treatment is greater than the calculated headroom value, then the new treatment will not be cost-effectiveness.

$$Headroom \leq \lambda \Delta QALY - \Delta Cost^{\#}$$

$$VBP_{\text{cumulative}} = Headroom$$

$$VBP_{\text{annual}} = \frac{r_d(Headroom)}{1 - (1 + r_d)^{-T}}$$

Equation 4: Calculating the value-based price through headroom analysis. $\Delta Cost^{\#}$: healthcare costs without new treatment costs, r_d : discount rate used in cost-effectiveness model, T: number of years on therapy

Headroom can be interpreted as the maximum monetary amount that drug manufacturers can charge per patient over the course of their treatment while being cost-effective based on payers' WTP for health outcomes. We refer to this estimate as the cumulative value-based price ($VBP_{\text{cumulative}}$), which can be annualized (VBP_{annual}) using the annuity formula (Equation 4). An annuity is a financial product that pays out a fixed stream of payments to individuals over a defined period. The annual payments made by

payors during the period where patients are treated can be viewed as an annuity provided to the drug firm until the treatment is complete.

2.4 Real options analysis to support development decisions

Drug manufacturers primarily rely on funding from for-profit investors – e.g. shareholders – to finance drug development projects.⁴⁰ Drug development decisions therefore focus on maximizing shareholder wealth in terms of free cash flow (FCF), which is calculated according to [Equation 5](#). Estimates of FCF can be determined using financial valuation techniques.^{16,30,38–41} Scientific, epidemiological, and clinical literature, along with regulatory and market data, are considered when evaluating the risk-reward profiles of drug development programs.^{16,38}

$$FCF = \text{Cash from Operations} - \text{Capital Expenditures}$$

Equation 5: Free cash flow (FCF) calculation.

The financial valuation models commonly used to support drug development decisions are risk-adjusted net present value (rNPV) and real options analysis, where the former is more widely adopted because it is simpler to analyze and understand.^{16,30,38} As described in [Equation 6](#), the risk-adjusted net present value (rNPV) approach takes the sum of forecasted FCFs that have been discounted by investors' cost-of-capital (r , opportunity cost of the investment) and drug development risks (θ , e.g., clinical trial success).^{30,57}

$$rNPV = \sum_{t=1}^T \frac{\theta_t FCF_t}{(1+r)^t}$$

Equation 6: Formula for risk-adjusted net present value (rNPV). θ : probability of passing development phase, t : time, FCF: free cash flow, r : investors' cost-of capital.

In general, the rNPV method is said to underestimate the value of an early-stage drug candidate.^{16,30,58} Even though most rNPV estimates for early-stage drug candidates are negative, for-profit

investors continue to invest and profit from them.^{38,59} This suggests that the rNPV method is not useful in supporting decisions for early-stage development projects.

The limitation of the traditional rNPV method is that it does not sufficiently consider the following:

- 1) Payer requirements for cost-effectiveness^{26,40,55},
- 2) Flexibility (optionality) of drug development (i.e., management has options to stop or continue development)^{16,38},
- 3) Uncertainty in the market value of the drug candidate³⁰.

To address the 1st limitation, headroom analysis can be applied to assess commercial viability of early-stage drug candidates by estimating a value-based price that meets payer requirements for cost-effectiveness. The 2nd and 3rd limitation can be addressed using method of real options, which applies the Black-Scholes⁶⁰ option pricing to inform management decisions⁶¹. Real options analysis can be used to inform a wide variety of management decisions and is particularly useful when dealing with high levels of uncertainty and decision flexibility, such as R&D investments.^{16,38,49,58,62,63} Schwartz and Moon (2000)⁶² applies the real options approach to develop a partial differential equation to value of R&D projects, as well as investment policy (i.e., under what conditions to invest in the project). Other real option models using partial differential equations have been developed by Schwartz to support R&D investment decisions.^{49,64} Kellogg (2000)⁵⁸ among others^{16,30,38,63} have applied the binomial option pricing model to inform pharmaceutical R&D investment decisions.

A real option is a choice made available to a management team of a company regarding investment decisions^{16,38,58,59}. In context to drug development, real options analysis evaluates the option that management has on the drug development project rather than the NPV of the drug candidate itself. Options are non-obligatory contractual rights to buy or sell an asset (e.g., drug candidate) at a pre-specified price up to a certain expiry date (decision node). Each decision can be viewed as a call option,

which is the right to finance the next stage in development. The option value for a drug development decision considers the market value of the drug candidate with the required capital investment to continue to the next development stage.

With every option, management can decide whether or not to continue investing in developing the drug candidate. Real options analysis assumes that management would only go forward with development (i.e., exercise the call option) if the drug candidate is expected to generate a profit (i.e., positive FCF). Incorporating this rule-based logic is how decision flexibility (optionality) is priced into option value.

Decisions to invest in drug development projects are structured around clinical trials (Figure 8). Investors have options to continue financing development in light of new evidence generated from the previous phase, which can significantly change the estimated market value of the drug candidate^{49,58,63}. Real options analysis acknowledges that the underlying market value of the drug candidate changes based on new medical (e.g., clinical trials) and market data (e.g., competition, patient demographics). A measure of volatility is incorporated to estimate upper and lower market value estimates (Figure 10, top). Option value therefore considers both the upper and lower estimates using risk-free probabilities based on the risk-free interest rate.

A simple example comparing rNPV and real option valuation methods is illustrated in Figure 9. Suppose management is faced with a decision to invest \$5 MM to develop a phase 3 drug candidate. The market demand for the drug is stochastic and, if approved, the risk-adjusted market value can be either \$40 MM or \$10 MM. To realize this value, the drug product must be launched at a cost of \$20 MM. The rNPV method does not consider decision flexibility and assumes the drug will be launched even if it is expected to generate a loss of -\$10 MM. In reality, management would avoid incurring a loss by not launching the drug if new information gained through phase 3 trials indicated a negative financial outcome. By not launching the drug at $t=1$, the company is in a net neutral position of \$0 ($V_{1,2}$) rather than

Phase 3 (t=0)

Invest? (go/no go)

$rNPV_{0,1}: -\$5 \text{ MM} = \$0 \text{ MM} - \$5 \text{ MM}$
 $V_{0,1}: \$5 \text{ MM} = \text{Max} [(\$10 \text{ MM} - \$5 \text{ MM}), 0]$

Drug Launch (t=1)

$rNPV_{1,1}: \$20 \text{ MM} = \$40 \text{ MM} - \$20 \text{ MM}$
 $V_{1,1}: \$20 \text{ MM} = \text{Max} [(\$40 \text{ MM} - \$20 \text{ MM}), 0]$

$rNPV_{1,2}: -\$10 \text{ MM} = \$10 \text{ MM} - \$20 \text{ MM}$
 $V_{1,2}: \$0 \text{ MM} = \text{Max} [(\$10 \text{ MM} - \$20 \text{ MM}), 0]$

```

graph LR
    A["Invest? (go/no go)  
rNPV0,1: -$5 MM = $0 MM - $5 MM  
V0,1: $5 MM = Max [($10 MM - $5 MM), 0]"]
    B["rNPV1,1: $20 MM = $40 MM - $20 MM  
V1,1: $20 MM = Max [($40 MM - $20 MM), 0]  
P1,1: 50%"]
    C["rNPV1,2: -$10 MM = $10 MM - $20 MM  
V1,2: $0 MM = Max [($10 MM - $20 MM), 0]  
P1,2: 50%"]
    A --> B
    A --> C
  
```

In this example, the two valuation methods lead to different recommendations. The rNPV method calculates a loss of -\$5 MM and supports a decision to forgo investment (no go), whereas the real option method estimates a net gain of \$5 MM and supports the decision to invest. This difference in valuation estimates are primarily driven by incorporating decision flexibility in the real options valuation method but not for rNPV. For early-stage drug development projects, there are a series of decisions management teams must make as a drug candidate transitions from one phase to the next. This series of decisions can be incorporated through the binomial option pricing model (BOPM).

The binomial option pricing model was previously applied to value early-stage biotechnology companies by Kellogg *et al.*⁵⁸ The BOPM structures the investment in early-stage drug candidates into a series of call options referred to as compounded options^{16,30,58,63}. The general rule-based logic pertaining to options is shown in Equation 7. The value of an option on an asset (e.g., drug) now is based on what the asset will be worth in the future. The BOPM considers decision flexibility. We assume that

management will only invest in development if the risk-adjusted market value of a drug candidate ($\theta_t A_{t,k}$) is greater than the development cost (S_t , i.e., capital expenditures) for a particular phase. The corresponding option value is the net positive difference between $\theta_t A_{t,k}$ and S_t . If $\theta_t A_{t,k} < S_t$, then management will forgo investment and the option is valued at \$0.

$$V_{t,k} = \text{Max}[(\theta_t A_{t,k} - S_t), 0]$$

Equation 7: Binomial option pricing model algorithm. Project value (A) is adjusted by the expected probability (θ) of clinical development success at each phase and subtracted by development cost (S_t). Options are valued at every time point (t) and every scenario (k) within each time point and is based on the future value at the next stage.

For early-stage drug candidates, management has series of decisions ($V_{t,k}$) to make throughout the development process. At every decision node along the development process, management has newly generated evidence on the technology along with the option (V_t) to continue or halt development. The newly generated evidence is assumed to increase or decrease the market value of the drug by a measure of volatility (σ) that reflects the uncertainty in the market value of the underlying drug candidate ($A_{t,k}$). The possible market values ($A_{t,k}$) the drug candidate can attain increases exponentially with time as a result of incorporating uncertainty in market value (Figure 10).

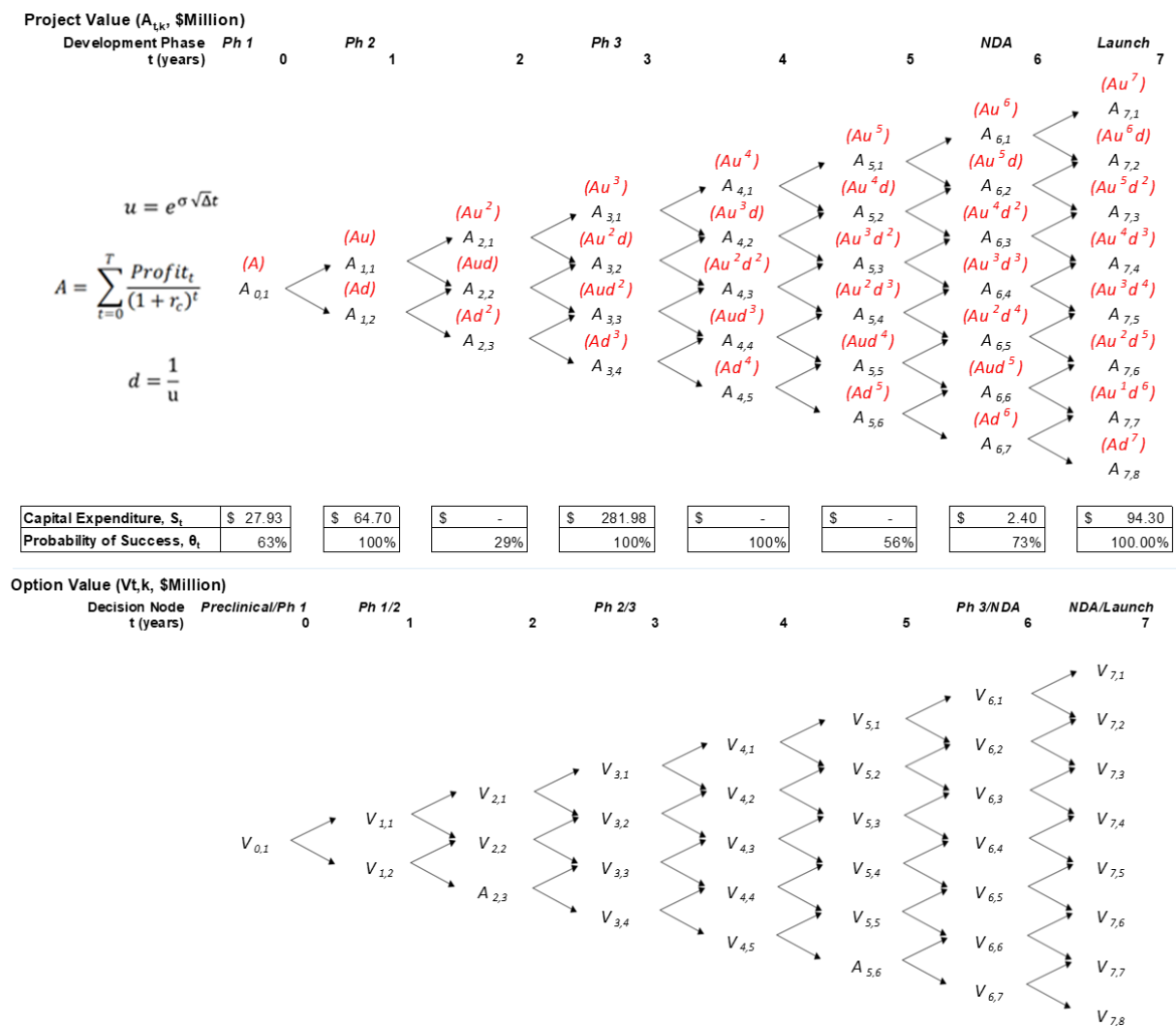


Figure 10: Asset and option values in a binomial lattice. The market value of the drug development project (asset) can be adjusted upwards (u) or downwards (d) based on a volatility measure (σ). Options values ($V_{t,k}$) are estimated based on the market value ($A_{t,k}$), development costs (S_t , capital expenditures), and risks (θ_t). Ph: development phase, NDA: new drug application.

Options (V_t) are exercised at a specified expiry date (i.e., the decision node). Exercising the option to continue investment allows management to gain new information about the drug candidate, as well as the rights on the option to finance the next development phase.¹⁶ For example, if a decision was made to finance phase 3 development (i.e., $V_{3,k}$ was exercised), positive results provides decision-makers the option ($V_{6,k}$) to file a new drug application (NDA). Similarly, investing in phase 2 clinical trials ($V_{1,k}$)

buys the option to acquire the future option to invest in phase 3 trials ($V_{3,k}$). These are referred to as iterated compound options, nested options, or multi-stage options.³⁰

The option (V_t) to invest or disinvest in a drug development project considers the financial benefits generated from the approved drug and the capital expenditures required to sell it on the market.^{16,38,62} To calculate option value, the market value of the drug candidate (A_t , Asset value) must first be estimated at every time point and adjusted by corresponding development risks (θ_t). The market value of the drug candidate (A_t) is based on the profits from future sales revenues (Equation 8). The risk-adjusted market value of the drug candidate ($A_t\theta_t$) is then compared against the capital expenditure (S_t) required to determine if exercising the option will generate positive FCF. It is important to note that in the BOPM, the FCF to calculate the market value of the drug candidate (A_t) excludes capital expenditures pertaining to drug development (S_t) because they are considered later when calculating option value (V_t).

$$A_t = \sum_{t=0}^T \frac{FCF_t}{(1 + r_c)^t}$$

Equation 8: Calculating the market value of the drug development project. The drug development project or drug candidate is valued by taking the present value of future free cash flows (FCFs) generated from sales revenues that are projected out until time T and adjusted by the investors' cost of investment capital (r_c).

The binomial option pricing model is a simplification of the Black-Scholes⁶⁰ option pricing model and requires similar assumptions including perfect liquidity, no arbitrage, and a constant risk-free rate (r_f). The option pricing model assumes that the market value on the underlying asset (A_t) is log-normally distributed, which is how the volatility measure is derived.^{16,58,63} Although some assumptions cannot be met in a real options context (e.g., perfect liquidity), the model can still be applied to inform management decisions.^{16,30,63}

$$u = e^{\sigma\sqrt{\Delta t}}$$

$$d = 1/u$$

Equation 9: Upward (u) and downward (p) asset price ($A_{t,k}$) adjustments using σ .

The model assumes that the market value of the drug candidate (A_t) fluctuates in a Brownian motion (σ , volatility), and its upper and low limits are represented through a binomial lattice (Figure 10). The market value can move upwards (u) and downwards (d) according to a measure of volatility (σ) that represents the log-normal standard deviation in the market value of the drug candidate (Equation 9).⁵⁸ This volatility measure can be estimated in reference publicly-listed firms with comparable products.^{16,58,63} The different scenarios (k) of market values at each time point (t) represent the distribution of market values the drug candidate (A_t) can command throughout the development process.

The BOPM projects the upper and lower market values of a drug candidate (A_t) at every possible scenario (k) and time point (t) up until product launch. From product launch onward, the market value of the drug is assumed to be more predictable given that the drug has received market approval. Sales revenues projected from the start of drug launch are discounted back to the initial decision point with the investors' cost-of-capital (r_c). From there, the market value at t_0 is adjusted by the upward and downward factor up until product launch (t_7) to provide the range of possible values throughout the development process where decisions need to be made.

Using the range of market value estimates for the terminal nodes, options are priced starting from the terminal decision nodes ($V_{7,t}$) of the binomial lattice based on their corresponding asset values ($A_{7,t}$). In this example, the terminal options are based on the decision to invest in launching the approved drug at Year 7 (Figure 10). An example is shown in Equation 10.

$$V_{7,1} = \text{Max} [(100\% \times A_{7,1} - \$94.3), 0]$$

Equation 10: Example option value ($V_{7,1}$) calculation at a terminal decision node.

Once all options are valued at each terminal node (Year 7), the preceding series of options in Year 6 are priced recursively from options in Year 7 as described in [Equation 11](#). This means that all preceding options from the terminal options can be viewed as nested options.³⁰ The value of a nested option considers two future option values (e.g., $V_{6,1}$ can change to $V_{7,1}$ or $V_{7,2}$) based on the upward or downward change in the market value of the drug candidate.

$$V_{t,k} = \text{Max} (\Theta_t [V_{t+1,k} * p + V_{t+1,k+1} * (1 - p)] e^{-r_f \sqrt{\Delta t}} - S_t, 0)$$

Equation 11: Calculating options on future options (i.e., nested options). Nested options are based on a risk-free probability (p) of realizing two possible option values (upper and lower value) using the risk-free rate (r_f).

Future options have a risk-neutral probability (p) of realizing a higher value, or a lower value with a probability of 1-p. Risk-neutral probabilities are probabilities that does not consider risks by using the risk-free rate (r_f). Risk-neutral probabilities (p) are applied to value options under the assumption of no arbitrage and that option values are independent of investors' risk preferences.⁵⁸ The probability of a future option having a higher value is calculated as described in [Equation 12](#). All option values are adjusted for development and commercialization risks (Θ_t), as well as time value of money using the risk-free rate (r_f). This iterated valuation process is repeated until the initial option ($V_{0,1}$) is priced.

$$p \text{ (risk - neutral probability)} = \frac{e^{-r_f \sqrt{\Delta t}} - d}{u - d}$$

Equation 12: Calculating the risk-neutral probability of an option being valued higher (u) or lower (d) in the future using the risk-free rate (r_f).

The objective of the BOPM is to value the initial option to invest in development – not necessarily to value future options. However, the initial option value is estimated recursively based the

range of terminal market values of the drug candidate ($A_{t,k}$) when it is ready for launch. This implies that the BOPM assumes the drug candidate completes development and launches when estimating the terminal market values. The estimated options after the initial decision node are valid only if the drug candidate passes through every development phase and is financed regardless of profitability, which is further discussed in [Chapter 5](#).

2.5 Value-based real options analysis framework

The market for medical care is dynamic due to uncertainties, in part, involving the effectiveness of the treatment, pricing, the health of the patient population, market conditions, the payers' willingness to pay, and the wealth of a nation.⁶⁵ The volatility in the market value of the drug candidate also involves such uncertainties and should be captured when evaluating in pharmaceutical R&D projects. We propose a decision framework that integrates real options and cost-effectiveness analyses to better consider the uncertainties underlying the healthcare market when evaluate drug development and commercialization strategies. We refer to this as the value-based real options analysis (VB-ROA) framework ([Figure 11](#)). The VB-ROA framework leverages cost-effectiveness analysis to better consider economic drivers of drug value. The VB-ROA framework considers the uncertainties underlying the healthcare market through the volatility (σ) estimate used to express the variance in the market value of the drug candidate.

The VB-ROA framework supports decisions from an industry perspective to develop cost-effective therapies that meet the needs of payers while ensuring profitability for drug manufacturers. The VB-ROA framework was constructed in two stages:

1. Value-based drug price (VBP) was estimated using headroom analysis derived from a probabilistic Markov model assuming a payer WTP of \$50,000 per quality-adjusted life year (QALY) and 3% discount rate (r_d) [[Chapter 3](#)].
2. Real options analysis (ROA) via the binomial lattice option pricing model was conducted to inform go/no go investment decisions using the VBP to forecast revenues discounted at a cost

of capital (r_c) of 15% and adjusted for clinical development risks (θ_t). The stochastic variable (σ) underlying the option value is based on the value-based price, as well as uncertainties in market size and operating costs [[Chapter 4](#)].

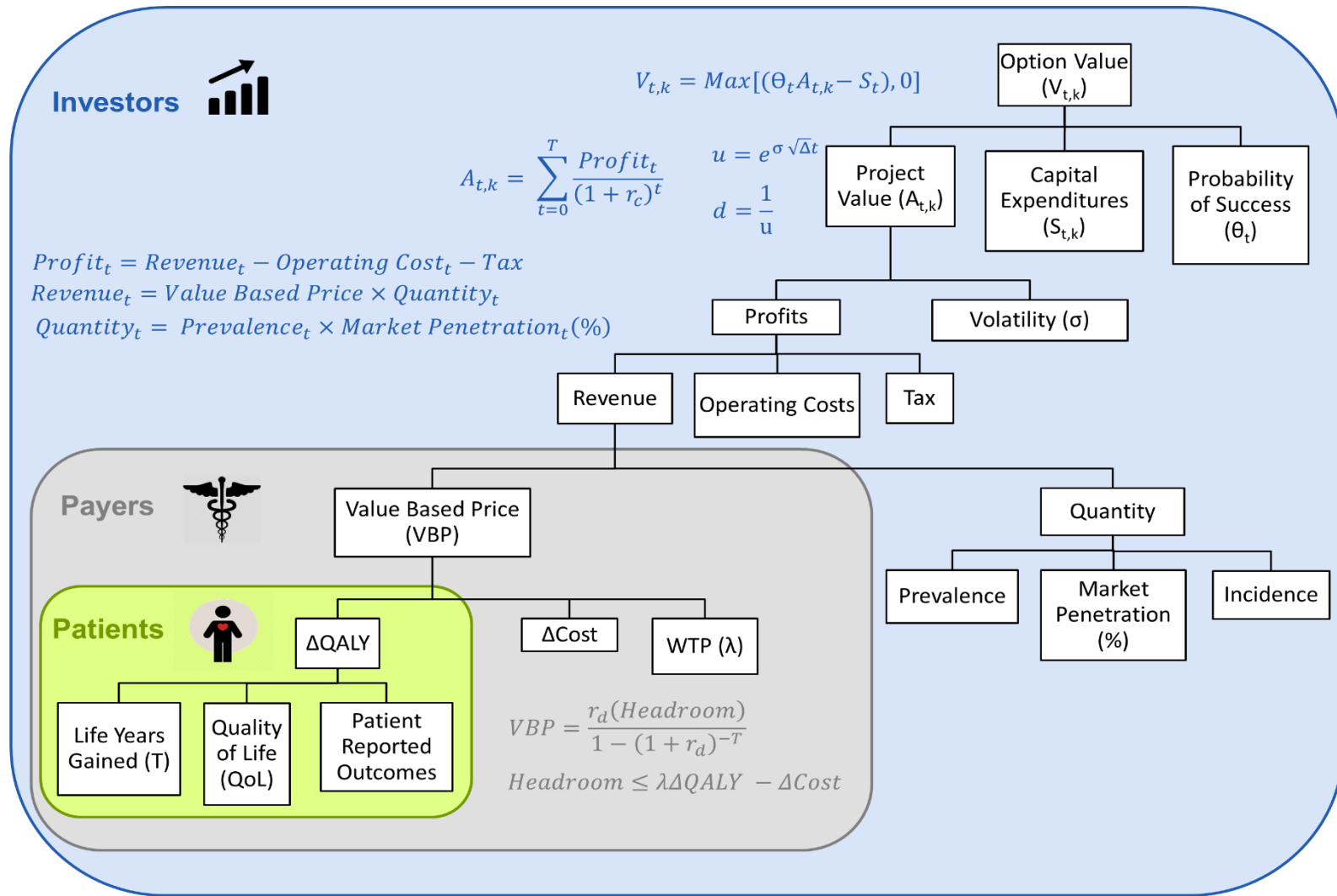


Figure 11: Overview of the value-based real option analysis (VB-ROA). The framework considers the perspectives of patients (orange), payers (grey), and for-profit investors/drug manufacturers (blue).

VB-ROA considers time value of money and health outcomes, where costs, health outcomes, and profits that are predicted to occur in the future are valued less than those that occur in the present. Cost and health outcomes are discounted to present value terms using the payers' discount rate of 3% (r_d).

Using a price estimated on headroom analysis functions to constrain revenue projections on cost-effectiveness limits (i.e., payer's WTP per incremental health outcome). The size of the market as well as any changes to its growth and penetration should be in line with the prevalence and incidence of the patient population used in headroom analysis.

The volatility of the market value of a drug candidate is difficult to measure in practice given that they are innovative technologies with no precedent cases. Volatility can be estimated in reference to the financial history of comparable early-stage biotech companies. Comparability should consider the disease indication and the patient population the technology is targeted towards. If market data is unavailable, then estimates can be derived through interviews with subject-matter experts (e.g., industry executives) through probability elicitation methods.^{66,67}

Annual financial reports of comparable companies and industry data should be referenced to estimate costs and revenues. Model parameters for the probability of development phase success and the capital expenditures required to finance each phase can be estimated from published studies on drug productivity trends. The value of this framework is that it offers decision-makers with a means to collectively consider diverse types of information as well as perspectives that are pertinent to drug development success.

The final output of the model is the option value to finance the development of a drug candidate based on the profitability of the drug when sold at the cost-effective price. A positive option value suggests that going forward with the development will generate a positive net present value (NPV) under a value-based price. A worthless option suggests that investing in development will lead to negative

returns. The model tracks the drug development project in terms of future profits and cost-effectiveness outcomes to ensure the needs of both payers and for-profit shareholders/investors are satisfied.

CHAPTER 3. VALUE-BASED PRICE FOR AN EARLY-STAGE DRUG THAT PREVENTS HYPOGLYCEMIA

3.1 Study Objective

The study objective is to quantify the value-based price (VBP) of a phase 1 drug candidate (i.e., SSTR2a therapy) aimed at preventing hypoglycemia through an early cost-effectiveness analysis method (i.e., headroom analysis) from the United States (U.S.) payer perspective. In the next chapter, we use the VBP to project revenues in a financial valuation model (i.e., real options analysis) that informs drug development decisions.

3.2 Introduction

3.2.1 Clinical background

Cost-effectiveness analysis (CEA) has yet to be applied to supporting drug development decisions for early-stage technologies aimed at preventing hypoglycemia for type 1 diabetes (T1D) patients. Over 1.3 million people in the US suffer from T1D^{68–70}, a chronic disease that typically requires intensive insulin therapy (i.e., ≥ 3 insulin injections daily) due to the autoimmune-mediated destruction of pancreatic islet β -cells that prevents normal secretion of endogenous insulin.⁷¹ A frequent and significant risk to the insulin dependent T1D patient population is hypoglycemia: a condition with abnormally low blood glucose levels partly due to glucagon counter-regulatory deficiencies.^{71–73} In the US, up to 10% of deaths among people with type 1 diabetes are related to hypoglycemia.^{74,75}

Hypoglycemia may be symptomatic or asymptomatic, where symptomatic hypoglycemia can be further segmented into severe and non-severe cases. Hypoglycemic symptoms include cognitive impairments (e.g., autonomic, neuroglycopenic, general malaise) that can lead to seizure, coma, and death, depending on severity.^{76,77} T1D patients undergoing intensive insulin therapy are at risk of severe hypoglycemia – a life threatening event that can cause seizure, coma, and death.^{78,79} Hypoglycemia occurs in the daytime or evening (nocturnal). Nocturnal hypoglycemia (NH) occurs during sleeping hours (i.e.,

12:00 AM to 6:00 AM) and accounts for 15% to 50% of all cases.^{80,81} NH is more difficult to treat due to the inability to detect and manage low glucose levels while asleep.

Hypoglycemia can also be categorized in terms of blood glucose (BG) levels experienced⁷³. Level 1 hypoglycemia occurs when blood glucose levels drop between 3.0 – 3.9 mM. Level 2 hypoglycemia is a clinically meaningful outcome that occurs when BG drops below 3.0 mM. Level 3 hypoglycemia (i.e., severe hypoglycemia) occurs when symptoms are so severe that the patient requires 3rd party assistance to restore euglycemia and alleviate symptoms.

Recurrent hypoglycemia that is poorly managed can cause patients to have impaired awareness of hypoglycemia (IAH), which occurs as a result of reduced symptomatic and hormonal responses to hypoglycemia.^{72,77,81–85} Approximately 20% of the T1D population have IAH, which increases their risk of severe hypoglycemia by 6-fold.⁸² Reported rates of severe (Level 3) hypoglycemic events are low relative to the overall rate of hypoglycemia in T1D (up to 1.59 episodes per person-year), but has a significant impact on individual patients' quality of life and can even lead to death. In comparison, non-severe events (Level 2) are more frequent (40 to 137 events per person-year), but have a lesser impact on patients' quality of life on a per event basis.^{81,83,86} Nonetheless, preventing non-severe hypoglycemia is important to prevent future severe events that have a greater impact on patient health-related quality of life (HRQoL) and hospital costs.⁸⁷

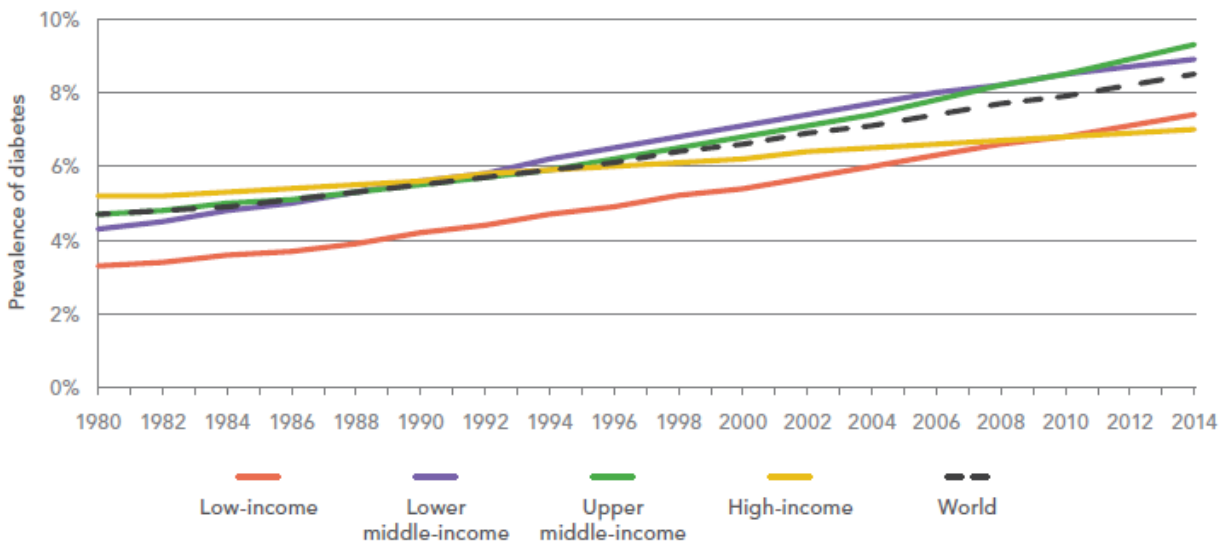


Figure 12: Trends in diabetes prevalence (1980-2014) by country income category. Source World Health Organization, 2016.⁸⁸

The economic cost of diabetes in the US comprised 20% of all healthcare expenditures (\$327 billion) in 2017.⁸⁹ This was a 26% increase from 2012 (\$260 billion) due to gradual increases diabetes prevalence (Figure 12) and cost of insulin therapies.^{88,89} Hypoglycemia has a significant impact on the overall cost of diabetes management including direct (e.g., ambulance services, emergency admissions, hospitalizations, physician visits, increased blood glucose measurements) and indirect (e.g., work productivity losses) costs.^{77,90} A 2015 study estimated that costs to manage severe hypoglycemia for US-based T1D patients with IAH were in between \$4.9 to \$12.7 billion per year.⁹¹

Although no preventative treatment for hypoglycemia exists, improvements in glucose monitoring, insulin delivery systems, and insulin-based pharmacotherapies are available to reduce the risk of occurrence for diabetic populations at risk of hypoglycemia. A clinical trial study, the HypoAna trial^{80,92}, reported a relative risk reduction of 0.29 (95% CI 0.19-0.84) and 0.06 (95% CI 0.02-0.10) in non-severe and severe hypoglycemia, respectively, when comparing the effect of insulin analogues vs. human insulin for a T1D cohort with recurrent severe hypoglycemia or IAH. Non-insulin adjunct

therapies with insulin treatment exist to preserve pancreatic islet β -cell functions, but evidence to support widespread clinical adoption is weak.⁹³

3.2.2 Somatostatin receptors and hypoglycemia

Somatostatin is a small peptide hormone that is dysregulated in insulin dependent diabetes. The hormone binds onto somatostatin receptors found on pancreatic alpha cells, which functions to inhibit the release of glucagon, and subsequently, glucose. Suppressing glucagon secretion in the pancreas has been shown to prevent recovery from hypoglycemia.^{94,95} A somatostatin receptor type 2 antagonist (SSTR2a) functions to block the native hormone from the docking onto somatostatin receptors along the surface of pancreatic alpha cells. Preclinical studies have shown that blocking the somatostatin type 2 receptors can reverse the dysregulated glucagon system by enabling the release of glucagon to stimulate the liver to release glucose.⁹⁴⁻⁹⁷

It is hypothesized that developing an SSTR2a that prevents hypoglycemia can improve patient health outcomes and reduce healthcare expenditures associated T1D. Patient health-related quality of life is likely to improve due to the reductions in hypoglycemia⁹⁸, as well as reduce the amount of healthcare resources spent on managing unwanted symptoms. The relevance of our choice to evaluate an SSTR2a technology using the VB-ROA framework is supported by an existing commercial development of a therapeutic in this category.

Zucara Therapeutics Inc. is a biotechnology company that is currently developing a novel peptide that targets somatostatin type 2 receptors to prevent hypoglycemia in people with diabetes, with an initial focus on nocturnal hypoglycemia. The SSTR2a is a first-in-class drug candidate currently in preparation to enter phase 1 clinical trials.⁸⁶ This technology area is at the correct stage of development to reflect the utility of the VB-ROA framework, facing the risks and uncertainties of a novel first-in-class agent in early stage development.

As drug candidates prepare for phase 1 studies, decision-makers in drug development need to evaluate the commercial and economic viability of the product to support the decision to continue development as well as construct development strategies. Estimating the future value-based price of a SSTR2a drug would help define the rationale to develop this early-stage technology.

3.3 Methods

The value-based price was enumerated via headroom analysis using a Markov model ([Figure 13](#)). Markov models are used to assess long-term cost-effectiveness of therapies for chronic diseases, such as cancer and diabetes. It is an analytic framework that is commonly used in decision analysis and economic evaluations of healthcare interventions.⁹⁹ They are stochastic processes where simulated patients move from one health state to another based on transition probabilities. The Markov model health states must be mutually exclusive and collectively exhaustive such that each individual patient in the model can be in only one state at any given time.

Markov models without tunnel states are memoryless, which means that the transition probability from the one state to another is not conditional on the previous health state.^{99,100} Simulated individuals either move between health states or stay in the same state at discrete time intervals (i.e., cycles). The time spent in a particular health state is associated with a cost and a health outcome, which are aggregated for the patient population over subsequent cycles. The incremental costs and effects are compared against λ to assess cost-effectiveness.

Headroom analysis applies cost-effectiveness analysis to calculate the incremental monetary value (i.e., headroom) gained from using a new therapy compared to usual care that takes the perspective of payers. The headroom can be interpreted as the maximum amount that drug manufacturers can charge payers for the drug to be cost-effective.

3.3.1 Target product profile

Although an early stage product in this new therapeutic category is currently in development, the performance targets for the product considered here was developed more generally, with assumptions developed from benchmark data from literature sources. This headroom analysis assumed a target product profile (TPP) for the SSTR2a drug candidate as described in [Table 1](#). TPPs facilitate communication between drug manufacturers and stakeholders regarding drug labelling claims.¹⁰¹ The TPP for the SSTR2a treatment was developed using assumptions based published literature and publicly available information, where possible.

The main value proposition of an SSTR2a treatment is its ability to reduce the frequency of symptomatic hypoglycemia (i.e., non-severe daytime, non-severe nocturnal, and severe hypoglycemia). Therefore, the indication was assumed to be for symptomatic hypoglycemia and the target population was T1D patients with a recent event. The target reductions in symptomatic hypoglycemia were based on the observed efficacy of usual care (i.e., basal-bolus insulin) and a report published by the American Diabetes Association Workgroup on Hypoglycemia outlining clinical meaningful improvements in managing hypoglycemia for T1D patients.¹⁰² The improvements in patient HRQoL were also included as secondary clinical endpoints given the association between hypoglycemia and patient quality of life outcomes.⁹⁸

Table 1: Target product profile for an SSTR2a drug candidate aimed at preventing hypoglycemia for type 1 diabetes patients.

Description	Target Product Characteristics
Indication	Adjunct to insulin therapy to prevent symptomatic hypoglycemia (i.e., daytime, nocturnal, and severe) for type 1 diabetes patients.
Patient population	type 1 diabetes patients with recent episode(s) of symptomatic hypoglycemia
Route of administration	Subcutaneous injection
Dosage form	Solution for once-daily injection
Pharmacokinetics	Suitable half-life to allow for daily administration
Target endpoints ¹	Relative risk of 0.469 (0.357, 0.616) non-severe symptomatic (Level 2, <3.0 mmol/L) and 0.774 (0.141, 1.458) severe hypoglycemia (Level 3)
Secondary outcome measures	Patient quality of life (EQ-5D), impaired hypoglycemia awareness (IAH, Gold score)

¹Relative risk reported as mean (95% CI).

The SSTR2a was assumed to be a peptide, as the majority of drugs acting on this target including approved agents for other indications (e.g. octreotide) and a preclinical compound shown to prevent hypoglycemia in animal models^{96,97} are cyclic octapeptides. Given this, the drug formulation (dosage form) was assumed to be in a solution form for subcutaneous injection similar to insulin therapies. The dosage form was assumed to allow for once-daily administration. These product characteristics are also similar to Zucara's intended approach to SSTR2a clinical development.¹⁰³

3.3.2 Model structure

The cost-effectiveness model was constructed in compliance to best practice guidelines, where possible.^{104–107} The model structure was informed through a review of previously published cost-effectiveness models on insulin analogue therapies for T1D patients that considered hypoglycemia as part of their analysis.^{108,109} Markov models were mostly used given that it is a chronic condition and the technologies have long-term health benefits. Model structures for diabetes vary in complexity where simple models have two states and others that are more complex.¹⁰⁸ For example, the CORE Diabetes model is comprised of 17 inter-dependent sub-models that each have several health states nested within it to simulate diabetes progression and several comorbidities.¹¹⁰

In this study, the cost-effectiveness model for headroom analysis was constructed using a Markov model with state-dependent transition probabilities as shown in Figure 13. Memory was not incorporated into the Markov model through tunnel states due to the lack of evidence and data needed to populate the model. The Markov model has a 1-year cycle length and consists of three health states: T1D with IAH (state 1, S1), T1D without IAH (state 2, S2), and the terminal state of death (state 3, D). Health states S1 and S2 are a stratification of the T1D population based on IAH prevalence reported in literature, which is approximately 20% of the T1D population.⁸² Therefore, the model starts with 20% of the T1D population with IAH (S1) and 80% without IAH.

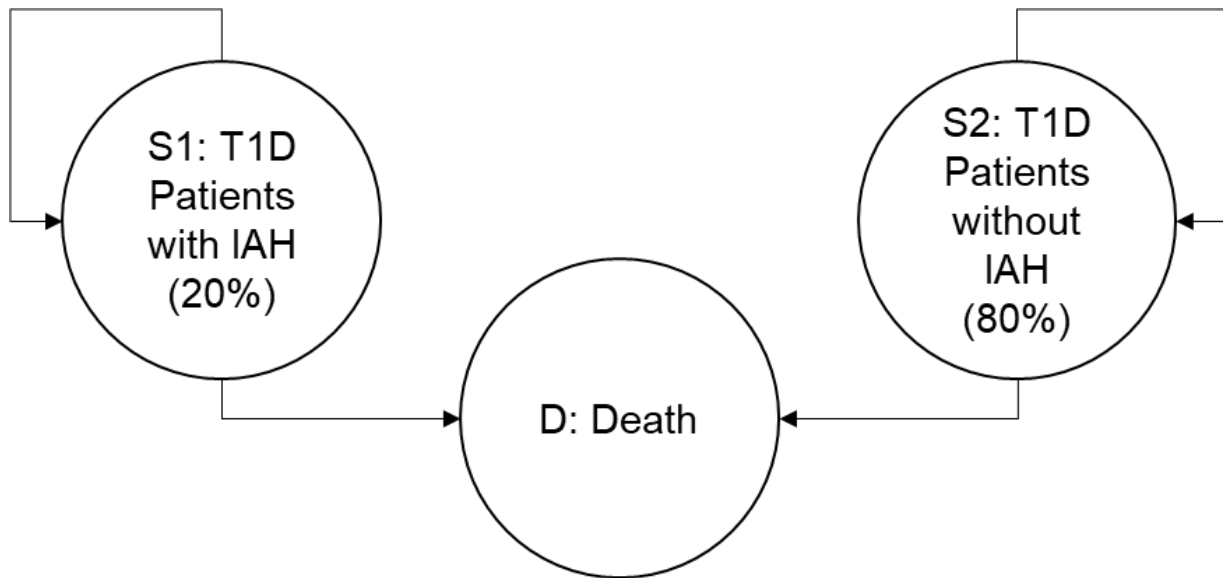


Figure 13: Markov model schematic for the headroom analysis. Patient population was segmented into two groups with different health states where one segment has IAH (S1) and the other does not (S2).

The model begins with a clinical decision to treat patients with either usual care (basal-bolus insulin, T_0), or a new treatment (basal-bolus insulin with SSTR2a as adjunctive therapy, T_x). Both treatment pathways have the same number of health states. At the start of every cycle, simulated patients either remain in the same health state or transition into the terminal state of death (D) using transition

probabilities. Transition probabilities to enter the terminal state of death were estimated using US age-specific mortality data¹¹¹ and the relative risk of death for T1D patients compared to the general population¹¹² (Table 2). Patients that transition to death remain in the absorbing state and do not incur any costs or changes in QALYs. The model assumed no state transitions between states S1 and S2 due to the lack of empirical data (Figure 13).

The model simulates incremental differences in health benefits (Δ QALY) and costs (Δ Cost[#]) associated with managing T1D and hypoglycemia across two treatment alternatives: insulin therapy (T_0 – usual care) vs insulin therapy with SSTR2a (T_x – new treatment). Health states S1 and S2 track costs and health outcomes pertaining to living with T1D (e.g., daily insulin therapy, blood glucose measurements), as well as, managing symptomatic hypoglycemic events (i.e., non-severe daytime, non-severe nocturnal, and severe events). Other complications associated with hypoglycemia (e.g., cardiovascular, neuropathy) were not considered in this model because the assumed value proposition of the therapy was to prevent hypoglycemia and improve patient HRQoL outcomes while reducing healthcare costs due to symptomatic events.

Incremental costs (Δ Cost[#]) between the two treatment alternatives were from the perspective of US payers. The model considers only direct medical costs pertaining to T1D, which includes costs for insulin therapy and managing hypoglycemic symptoms as shown in Table 3. However, the costs associated with new treatment were not included in the analysis per the headroom method.^{39,56}

Incremental effectiveness was measured in quality-adjusted life years (Δ QALY). The analysis used the QALY as the primary outcome measure given that a majority of CEA for insulin analogues measured effectiveness in terms of QALYs.¹⁰⁸ It is assumed that all patients have the same baseline HRQoL measure at the start of the model. For every hypoglycemic event encountered, patients' baseline quality of life are adjusted by HRQoL deductions associated with a single occurrence of hypoglycemia.

Costs and health benefits were adjusted by a payers' discount rate (r_d) of 3% per year, as per US guidelines by the second panel on cost effectiveness (case 1).¹⁰⁷ A lifetime horizon was chosen for the baseline model, which was assumed to be 40 years. We assumed a lifespan that ends by 85 years of age, and the average age of patients were 45 years old based on clinical trial data used for the model.

The primary outcome is the value-based price derived from the calculated headroom ([Equation 4](#)). The value-based price is based on payer willingness-to-pay threshold (λ) of \$50,000 USD per QALY gained, which is a common threshold used in other CEA of T1D studies.¹⁰⁸ Statements of commercial viability are based on price comparisons of similar treatments, as well as subsequent financial valuation analysis of the business opportunity (see [Chapter 4](#)).

3.3.3 Clinical parameters

The clinical model for T1D was constructed using data found in published literature as summarized in [Table 2](#). The transition probabilities from health states S1 and S2 to death (D) were calculated by using age-specific mortality statistics published in the 2014 US Census¹¹¹, which were adjusted by the relative risk of mortality for T1D patients relative to the general population reported in a meta-analysis by Lung *et al.* (2014)¹¹².

To populate data pertaining to patient-level disease trajectory (i.e., hypoglycemia incidence) and insulin therapy, we referenced two clinical trials that assessed efficacy of insulin analogues to manage blood glucose and hypoglycemia for T1D patients. As a result, clinical parameters across states S1 and S2 differed in terms of hypoglycemia rates ([Table 2A](#)) and insulin treatment doses ([Table 3B](#)). To model T1D patients with IAH (S1), we referenced the HypoAna trial^{92,113}, which is a multicenter, prospective, and randomized study that evaluated the effectiveness of insulin analogues for a T1D cohort that either had impaired awareness (38%) or were fully unaware (56%) of hypoglycemic symptoms. For T1D patients without IAH (S2), we referenced the BEGIN BB T1 trial¹¹⁴, which is a multinational clinical trial

comparing the efficacy of insulin analogues for a T1D cohort with no recent severe hypoglycemic events and are not considered to have IAH.

Health benefits were measured in terms of the QALY metric, which ranges from 1 (perfect) to 0 (death). HRQoL weights were obtained from a time trade-off survey by Evans et al (2013)¹¹⁵ that asked the general population to trade off a portion of their remaining lifespan for improvements in the current quality of life. For every occurrence of symptomatic hypoglycemia, there is a reduction from a patient's baseline quality of life. All patients in the model had a baseline HRQoL measure of 0.844 along with HRQoL weight deductions that correspond to a single hypoglycemic event with different severities (Table 2D).¹¹⁵

Table 2: Summary of clinical parameters inputted into the cost-effectiveness analysis.

Clinical Parameters	Mean (95% CI)	Distribution Assumed	Hyperparameters	Source
A. Hypoglycemia Incidence (events/person-year)				
<i>T1D with IAH (S1)</i>				
Non-Severe Hypoglycemia				
Daytime	53	Gamma	α : 4530 β : 0.0117	113
Nocturnal	6.4	Gamma	α : 545 β : 0.0117	113
Severe Hypoglycemia	1.18	Gamma	α : 93 β : 0.0127	92
<i>T1D without IAH (S2)</i>				
Non-Severe Hypoglycemia				
Daytime	39.46	Gamma	α : 2846 β : 0.0139	114
Nocturnal	5.93	Gamma	α : 428 β : 0.0139	114

Clinical Parameters	Mean (95% CI)	Distribution Assumed	Hyperparameters	Source
Severe Hypoglycemia	0.39	Gamma	α : 28 β : 0.0139	114
B. Health State Transition Rates				
Relative Risk of Mortality	3.82 (3.41, 4.29)	Log-normal	N/A	111, 112
C. Relative Risk of Hypoglycemic Events (SoC & SSTR2a vs. SoC) for S1 and S2				
Non-Severe Hypoglycemia (Daytime & Nocturnal)	0.469 (0.357, 0.616)	Log-normal	N/A	102,116
Severe Hypoglycemia	0.774 (0.414, 1.458)	Log-normal	N/A	102,116
D. HRQoL Weights for S1 and S2				
Base Quality of Life	0.844 (0.839, 0.848)	Gamma	α : 684127 β : 0.00000123	115
Non-Severe Hypoglycemia				
Daytime	-0.005 (-0.004, -0.006)	Gamma	α : 384.16 β : 0.0000130	115
Nocturnal	-0.007 (-0.005, -0.009)	Gamma	α : 188 β : 0.0000372	115
Severe Hypoglycemia	-0.055 (-0.046, -0.065)	Gamma	α : 465 β : 0.000117	115

Given there is no clinical evidence on the SSTR2a's safety and effectiveness in humans, we defined a counterfactual (i.e., hypothetical scenario for drug performance in terms of HRQoL and quantity of life) based on benchmarks of minimally required effectiveness set by the American Diabetes Association (ADA) Workgroup on Hypoglycemia. The effectiveness of the new treatment (i.e., SSTR2a) compared to usual care (e.g., basal-bolus insulin) was assumed to be the same for patients with (S1) and without IAH (S2). Treatment effectiveness was measured in terms of relative risks (RR), which is a ratio

of hypoglycemia incidence rates ($\text{incidence}_{\text{newtreatment}}/\text{incidence}_{\text{usual care}}$). To quantify hypoglycemia incidence in the population receiving new treatment, hypoglycemia incidence for those receiving usual care were adjusted with the RR of SSTR2a.

According to the ADA, a clinically meaningful improvement in hypoglycemia management compared to standard care is a 10 – 20% reduction in severe and $\geq 30\%$ reduction in non-severe hypoglycemic events.¹⁰² To represent the effectiveness pertaining to standard of care, we referenced a clinical trial by Davies et al (2016) that evaluated the efficacy of newer insulin analogues (i.e., insulin degludec) against older analogues (i.e., insulin detemir).¹¹⁶ The reported relative risks (RR) from Davies et al (2016) were adjusted by the benchmark reductions in hypoglycemic events (i.e., 10% NSH and 30% SH), which gave a RR of 0.469 (95% CI 0.357, 0.616) and 0.774 (95% CI 0.414, 1.458) for non-severe and severe hypoglycemia, respectively (Table 2C).

3.3.4 Cost parameters

Costs were estimated based on data gathered from published literature and adjusted to 2018 US dollars. Only direct costs from a payer perspective were considered in the model, which includes healthcare resources associated with managing symptoms of hypoglycemia and basal-bolus insulin therapy (Table 3). Insulin costs were calculated based on the daily insulin dosage reported in the HypoAna trial^{92,113} and BEGIN BB T1 trial¹¹⁴ and prices of insulin detemir and insulin aspart reported by Thomas Reuters.¹¹⁷

Expected costs for hypoglycemia were calculated based on US healthcare budget impact studies, which include frequency and likelihood (%) of occurrences, as well as actual costs.^{118–120} Each cost item was adjusted with the probability of consuming these healthcare resources, and the expected costs were inputted into the model. The per event cost of non-severe hypoglycemia costs include an average of 3.9 extra blood glucose tests and a 13% chance of a general physician visit.

Costs for severe hypoglycemia were based on the assumption that the events required medical attention, not merely assistance from another person. This included the following cost items: ER admission, ambulance, inpatient, outpatient, general physician consultations, and nursing services. Glucagon injection costs were excluded when estimating SH event costs based on the approach taken in an economic impact study by Foos et al (2015).¹¹⁸ The study included glucagon injections for SH only when it required assistance from another person (e.g., oral ingestion of carbohydrate sugars), but excluded when the SH required medical attention (e.g., physician visits, ambulance, emergency).¹¹⁸

Table 3: Direct healthcare costs for hypoglycemic events and insulin therapy.

Costs (\$USD)	Frequency	Mean (SD)	%RSD	Distribution	Hyperparameters	Source
A. Adverse Events						
<i>Non-Severe Hypoglycemia (Daytime & Nocturnal)</i>						
Visit to GP	13.7%	\$51.00	N/A	N/A	N/A	118
Extra Blood Glucose Test	3.9 times	\$1.22	N/A	N/A	N/A	118
<i>Severe Hypoglycemia</i>						
ER Admission	17.0%	\$139.00 (\$217.67)	818%	Gamma	α : 0.0149 β : 1781	118,120
Ambulance	21.3%	\$214.00	N/A	N/A	N/A	118
Inpatient	24.0%	\$4,171.00 (\$12,805.17)	1136%	Gamma	α : 0.00775 β : 145452	118,120
Outpatient	20.0%	\$325.00 (\$471.42)	644%	Gamma	α : 0.0241 β : 3036	118,120
Visit to GP	26.0%	\$51.00	N/A	N/A	N/A	118
Nurse	13.0%	\$43.00	N/A	N/A	N/A	118
B. Insulin Usage (IU/kg/day)						
<i>T1D with IAH (S1)</i>						
Insulin Detemir	N/A	23.9 (12.0)	N/A	Gamma	α : 3.9667	92,113

Costs (\$USD)	Frequency	Mean (SD)	%RSD	Distribution	Hyperparameters	Source
Insulin Aspart	N/A	24.9 (13.4)	N/A	Gamma	β : 6.0251 α : 3.4529 β : 7.2112	92,113
<i>T1D without IAH (S2)</i>						
Insulin Detemir	N/A	27.3 (1.3)	N/A	Gamma	α : 420.25 β : 0.065073	114
Insulin Aspart	N/A	42.0 (2.0)	N/A	Gamma	α : 441 β : 0.095286	114
<i>Insulin Cost (per unit)</i>						
Insulin Detemir	N/A	0.15	N/A	N/A	N/A	117
Insulin Aspart	N/A	0.18	N/A	N/A	N/A	117
Injection Needles	N/A	0.30	N/A	N/A	N/A	117
Blood Glucose Test	N/A	1.63	N/A	N/A	N/A	119

N/A: not available due to lack of data

3.3.5 Sensitivity analysis

A number of sensitivity analyses were performed. We examined one-way sensitivity of model parameters regarding patient-level disease trajectory, costs, effectiveness, WTP, and discount rate by modulating the inputted parameters by $\pm 50\%$. For costs, we examined the sensitivity of costs pertaining to severe and non-severe hypoglycemia. Insulin costs were not sensitive to the value-based price since it does not change ΔCost as insulin costs are equal across treatment groups. In terms of effectiveness, we evaluated the sensitivity of inputs for IAH prevalence, HRQoL decrements for every hypoglycemic event, and the effectiveness (RR) of the SSSTR2a therapy at reducing hypoglycemia incidence.

Deterministic sensitivity analyses informing alternate scenarios important to decision-makers were conducted. These scenarios pertain to productivity costs, IAH prevalence, and hypoglycemia

incidence. Productivity costs are typically not included when using a payer perspective, but can be considered when taking a societal perspective as recommended as a 2nd base case by the 2nd panel on cost effectiveness.¹⁰⁷ Expected productivity costs for every NH and NSH event were estimated to be \$12.33 and \$24.40, respectively, using wages published by US Labor Statistics in 2017 and cost data published in literature.^{108,121}

Scenarios considered IAH prevalence diagnosed through different methods derived by Gold¹²², Clarke¹²³, and Pedersen-Bjergaard¹²⁴, along with corresponding SH incidence¹²⁵. Although IAH prevalence is generally regarded as 20% based on the Gold criteria, different diagnosis methods have led to differences in IAH prevalence and corresponding SH incidence. Lin et al reported IAH prevalence in a T1D cohort using the Gold, Clarke, and Pedersen-Bjergaard questionnaires, which were 33.3%, 43.7% and 77.0%, respectively¹²⁵. IAH or hypoglycemia unawareness identified by the Gold, Clarke, and Pedersen-Bjergaard method were associated with 6, 4.63 and 5.83-fold increases in risk of severe hypoglycemia, respectively.

Further scenarios inputting NH incidence measured through different methods were included in the analysis. Incidence of NH varies considerably depending on the measurement methods [self-monitoring blood glucose (SMBG) vs continuous-glucose monitoring (CGM)] used to detect events.⁸⁰ Nocturnal hypoglycemia has been under-reported in studies using SMBG tests, and the HypoAna study observed that CGM data reported 17 times more non-severe nocturnal hypoglycemia than SMBG methods.⁸⁰ SMBG requires patients to make sparse measurements of their blood glucose levels, whereas CGM is a medical device that takes continuous measurements of plasma glucose levels. CGM enables patients to take glucose measurements during sleep and SMBG measurements are limited to when the patient is conscious, which suggests SMBG is likely to be under-reporting NH incidence.

Probabilistic analysis was conducted on the model using distributions for model parameters as recommended by Briggs et al (2006)^{126,127}. To estimate the joint effect of parameter uncertainty on the

value-based price, a Monte Carlo simulation of 10,000 draws was performed. The use of Markov Model Monte Carlo simulations to estimate posterior probability distribution of the value-based price and other model outputs requires a Bayesian approach¹²⁸. Bayesian statistics interprets probability as a degree of belief in an event based on prior knowledge regarding an event. Since Bayesian statistics was applied, the uncertainty of the value-based price and other outputs were reported in terms of 95% credible intervals and standard deviation. For a 95% credible interval, the true value has a 95% probability of being within the interval.

Relative risks were assumed to be log-normally distributed since it is the standard assumption in epidemiological literature that the natural log of relative risk has a normal distribution.^{129–131} Relative risk (RR) estimates used in the model include: 1) RR of hypoglycemia (non-severe symptomatic daytime, nocturnal, and severe) in T1D patients on SSTR2a compared to usual care, and 2) RR of death in T1D patients compared to the general population.

Gamma distributions were assigned to represent uncertainty in cost-related parameters and hypoglycemia incidence rates as these parameters have intervals of 0 to infinity and are right-skewed.^{126,132} HRQoL weights were also assigned a gamma distribution according to NICE guidelines.¹³³ HRQoL weights are constrained within negative infinity (lower limit) and 1 (upper limit). Therefore, weights (w) were transformed into decrements ($1-w$) and fitted into a gamma distribution.

The CEAC was not generated for this analysis. This is because it is assumed that the new drug is always more effective and more cost-efficient. The estimated ICER will always be cost-effective because the any cost associated with the new treatment (e.g., drug price) is not considered in headroom analysis.^{56,134} Rather, the headroom analysis calculates the added value of using the new therapy, which can be used to estimate a cost-effective drug price.

3.4 Results

The characteristics of the patient cohort simulated from our model were taken from the referenced RCT studies and are summarized in [Table 4](#). The cohorts representing T1D patients with (S1) and without (S2) IAH were similar across most clinical characteristics including age, body mass index, and HbA1c levels.

Table 4: Patient cohort baseline characteristics.

Stratified patient cohort – Mean (SD)	S1: No IAH ¹¹⁴	S2: IAH ^{92,113}
Female (%)	44	37
Age (years)	41.7 (14.4)	54.7 (12.9)
Body mass index (kg/m ²)	23.7 (3.4)	25.0 (3.8)
HbA1c (%)	8.0 (0.9)	8.0 (1.0)
Duration of T1DM (years)	14.4 (9.7)	30.1 (13.2)
Treated with basal-bolus insulin regimen	Yes	Yes
Impaired Awareness of Hypoglycemia	No	Yes

Using the input parameter data from [Table 2](#) & [Table 3](#), the model recorded the ranges of parameter estimates used in a Monte Carlo simulation ([Table 5](#)). The expected mean (95% C.I.) cost for every severe hypoglycemic event was simulated to be \$257.21 (95% CI \$77.36, \$1,814.69). The cost for every non-severe hypoglycemic event, which includes a visit to a general physician and extra blood glucose tests, remained static at \$12.62 given there was no reported variance to reference.

The baseline model simulated the mean (95% CI) annual cost of insulin therapy for T1D with (S1) and without (S2) IAH to be \$4,312.98 (95% CI \$4,019.20, \$4,622.54) and \$ 2,970.86 (95% CI \$1,237.29, \$5,515.11), respectively. Differences in annual insulin costs are driven by differences in daily insulin dose requirements. However, lifetime insulin costs across treated and untreated groups were comparable. Lifetime insulin costs of \$82,950.84 (95% CI \$75,803.97, \$92,142.09) for those on new treatment and \$81,149.05 (95% CI \$74,008.87, \$90,344.42) for patients given usual care.

Table 5. Summary of simulated model inputs. HRQoL: health-related quality of life, RR: relative risk, T1D: type 1 diabetes.

	95% Credible Interval			
	Mean	SD	Lower Limit	Upper Limit
<u>Model Inputs</u>				
<i>Costs parameters (\$USD)</i>				
Annual cost of insulin therapy (incl. basal-bolus insulin, injection needles, and SMBG tests)				
T1D with IAH (S1)	\$ 4,312.98	\$ 153.17	\$ 4,019.20	\$ 4,622.54
T1D without IAH (S2)	\$ 2,970.86	\$ 1,116.19	\$ 1,237.29	\$ 5,515.11
Cost per hypoglycemic event				
Non-Severe (Daytime & Nocturnal)	\$ 12.62	N/A	N/A	N/A
Severe	\$ 257.21	\$ 1,178.44	\$ 77.36	\$ 1,814.69
<i>Effectiveness (RR) of new treatment</i>				
Non-Severe Daytime	0.470	0.033	0.408	0.538
Non-Severe Nocturnal	0.470	0.032	0.411	0.536
Severe	0.781	0.127	0.566	1.060
<i>HRQoL weights</i>				
Baseline	0.844	0.001	0.842	0.846
Non-Severe Daytime	-0.005	0.000	-0.006	-0.005
Non-Severe Nocturnal	-0.007	0.001	-0.008	-0.006
Severe	-0.055	0.003	-0.060	-0.050
<i>Hypoglycemic incidence (events/person-year)</i>				
T _x (new treatment)				
T1D with IAH (S1)				
Non-Severe Daytime	24.91	1.78	21.57	28.56
Non-Severe Nocturnal	3.01	0.25	2.55	3.51
Severe	0.92	0.18	0.62	1.32
T1D without IAH (S2)				
Non-Severe Daytime	18.55	1.34	16.05	21.28
Non-Severe Nocturnal	2.79	0.24	2.36	3.27
Severe	0.30	0.08	0.18	0.48

	Mean	SD	95% Credible Interval	
			Lower Limit	Upper Limit
T ₀ (usual care)				
T1D with IAH (S1)				
Non-Severe Daytime	53.00	0.79	51.45	54.56
Non-Severe Nocturnal	6.40	0.27	5.88	6.94
Severe	1.18	0.12	0.96	1.44
T1D without IAH (S2)				
Non-Severe Daytime	39.46	0.74	38.01	40.89
Non-Severe Nocturnal	5.93	0.29	5.38	6.51
Severe	0.39	0.07	0.26	0.55
Mortality				
Hazard Ratio (Death T1D)	3.82	N/A	3.41	4.29

¹negative values indicate savings in costs from using the new intervention.

N/A: not available, T1D: type 1 diabetes, HRQoL: health-related quality of life, N/A: variance estimates not available. All costs are in 2018 USD

3.4.1 Value-based price of an SSTR2a drug that prevents hypoglycemia

The mean (95% CI) value-based price for our SSTR2a treatment was estimated to be \$5,180 (95% CI \$4,437, \$5,956) per year per patient (Figure 14 & Table 6). This was based on an expected headroom of \$119,728 (95% CI \$102,569, \$1,374,673), which is the maximum value realized by payers for every patient using the new drug over a lifetime horizon (mean of 40 years). The headroom was calculated from λ of \$50,000 USD, expected incremental per-patient effectiveness (Δ QALY) of 2.31 (95% CI 1.99, 2.64) QALYs, and cost-savings (Δ Cost[#]) of \$3,999 (95% CI \$3,016, \$5,745) over the patient lifetime.

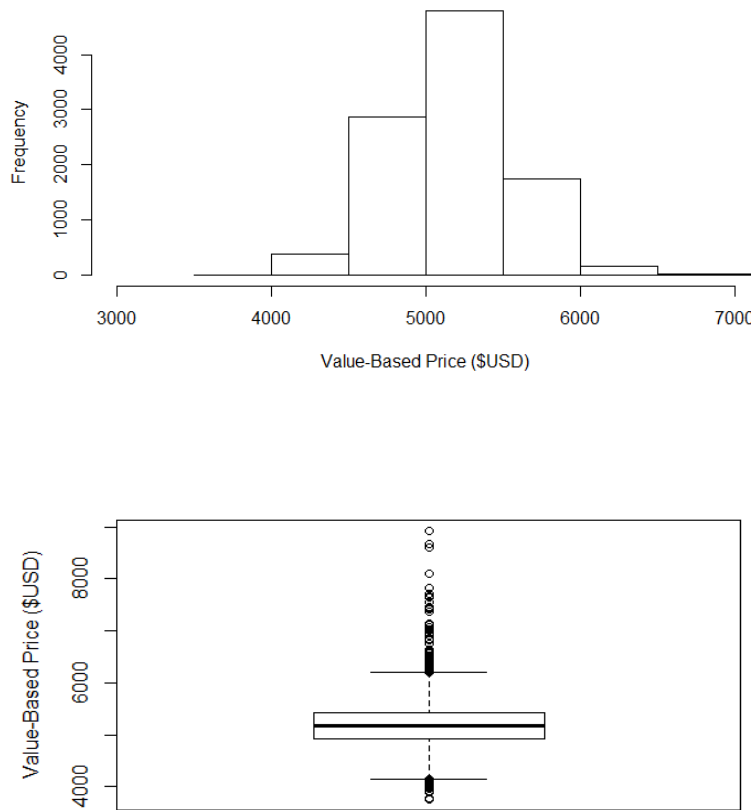


Figure 14: Probability distribution of the annual value-based price. Mean (95% C.I.): \$5,178 (95% CI \$ 4,437, \$ 5,956), top: histogram, bottom: boxplot.

The incremental gain in QALY of 2.31 (95% CI 1.99, 2.64) is attributed to the lower occurrences of hypoglycemia as a result of being treated with the SSTR2a. Compared to usual care, each patient on the new treatment avoids, on average, 2.0 (95% CI 0, 4.12) severe, 52.5 (95% CI 44.9, 59.9) nocturnal, and 367.7 (95% CI 319.7, 411.8) non-severe daytime hypoglycemic episodes over their lifetime. For every occurrence of hypoglycemia, T1D patients' baseline HRQoL weights, which was 0.844 (95% CI 0.842, 0.846), was adjusted by a disutility weight of -0.005 (95% CI -0.006, -0.005), -0.007 (95% CI -0.008, -0.005), and -0.055 (95% CI -0.060, -0.050) for non-severe daytime, nocturnal, and severe events, respectively.

Table 6: Value-based price and headroom analysis results for the SSTR2a drug candidate.

	95% Credible Interval			
	Mean	SD	Lower Limit	Upper Limit
<u>Model Outputs</u>				
<i>Value-Based Price (\$USD/year)</i>	\$ 5,179.73	\$ 398.11	\$ 4,437.39	\$ 5,956.05
<i>Headroom</i>	\$ 119,728.36	\$ 9,202.17	\$ 102,569.27	\$ 137,672.81
Δ Cost	-\$ 3,999.19	\$ 2,815.62	-\$ 5,744.93	-\$ 3,016.23
T _x (new treatment)	\$ 89,438.32	\$ 9,328.40	\$ 81,083.14	\$ 102,995.68
T ₀ (usual care)	\$ 93,437.51	\$ 11,404.93	\$ 84,758.00	\$ 108,545.27
Δ QALY	2.31	0.17	1.99	2.64
T _x (new treatment)	11.54	0.19	11.16	11.90
T ₀ (usual care)	9.23	0.21	8.80	9.64
Frequency of hypoglycemia				
Δ Non-Severe Daytime	367.7	23.5	319.7	411.8
T _x (new treatment)	326.1	23.4	282.5	374.0
T ₀ (usual care)	693.8	11.4	671.7	716.3
Δ Non-Severe Nocturnal	52.5	3.8	45.0	59.9
T _x (new treatment)	46.6	3.7	39.7	54.3
T ₀ (usual care)	99.1	4.0	91.5	107.0
Δ Severe	2.3	0.2	2.0	2.6
T _x (new treatment)	7.0	1.4	4.7	10.2
T ₀ (usual care)	9.0	1.1	7.1	11.2

Decreases in hypoglycemic events also translate to reduced costs with managing hypoglycemia. Payers save \$5,800.98 (\$4,813.09, \$7,531.64) on costs per patient lifetime as a result of avoiding \$5,303.24 (\$4683.71, \$5,869.18) non-severe and \$ 497.74 (\$49.86, \$2,196.29) severe hypoglycemic event-related costs. Overall costs were reduced since the cost of the new treatment is not considered in headroom analysis and no downstream costs increases were encountered in the model.

3.4.2 One-way sensitivity analysis

Figure 15 summarizes results from a one-way sensitivity analysis where model inputs used in the base case were adjusted by $\pm 50\%$ to observe its effect on the value-based price. Results indicate that payers' WTP (λ) was the most sensitive model parameter as a 50% adjustment would change the value-based price by $\pm 47\%$. Parameters corresponding to non-severe daytime hypoglycemic events [NSH (Day)] were the next most sensitive to the value-based price given its frequency was the highest compared to other forms of hypoglycemia. In particular, the value-based price was sensitive to parameters for NSH (Day) on HRQoL decrements ($\pm 37\%$), baseline incidence for T1D patients without IAH ($\pm 29\%$), and SSTR2a treatment effectiveness ($\pm 34\%$).

Other remaining parameters exhibited a $\leq 11\%$ impact on the value-based price after modulating the input values by $\pm 50\%$. Parameters associated with T1D patients with IAH (S2) were less sensitive to the price than T1D without IAH (S2) because the proportion of the T1D population with IAH is 4 times less than those without IAH. Parameters associated with nocturnal and severe hypoglycemia are not as sensitive to price as daytime events due to differences in the lower recorded frequencies in which they occur. Notwithstanding, the rate of reported nocturnal events can vary greatly depending on the method of detection.⁸⁰

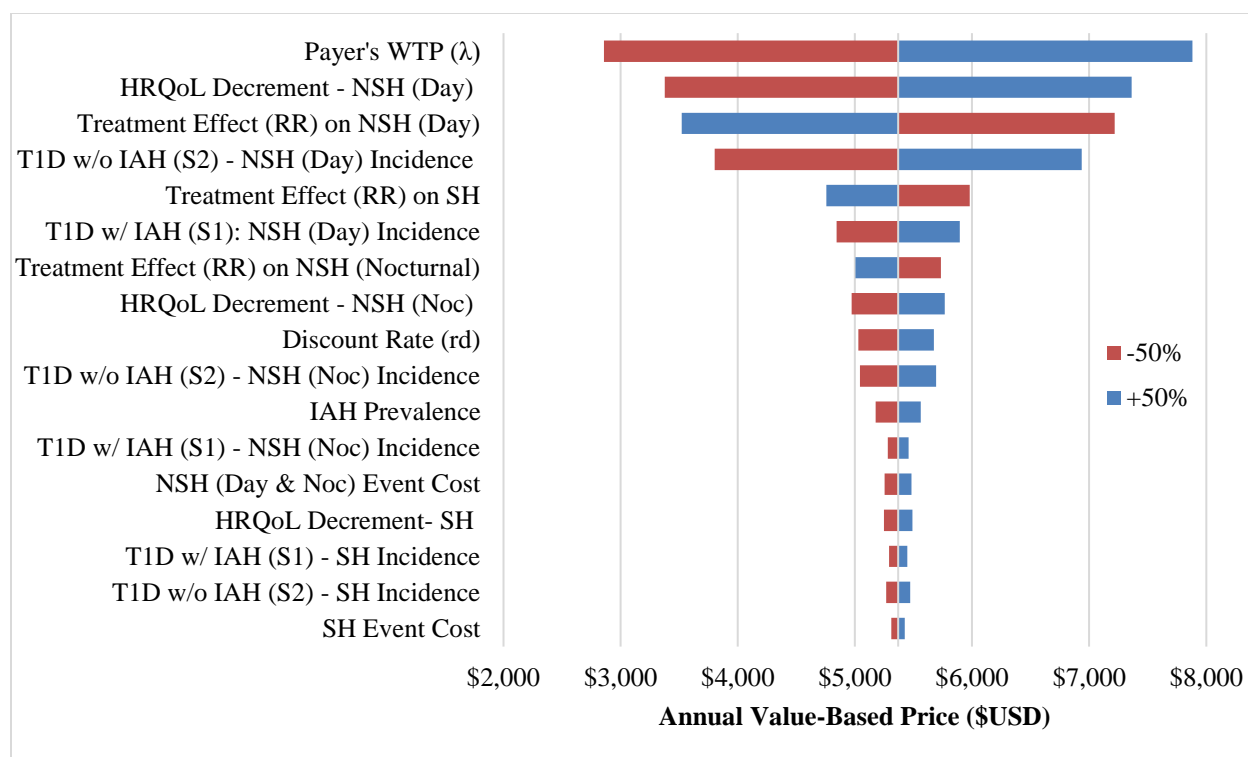


Figure 15: Tornado plot of one-way sensitivity analysis ($\pm 50\%$) on value-based price. Base case value-based price is \$5,369.30. T1D: type 1 diabetes, SH: severe hypoglycemia, NSH (Day): non-severe daytime hypoglycemia, NSH (Noc): non-severe nocturnal hypoglycemia, IAH: impaired awareness of hypoglycemia, HRQoL: health-related quality of life, RR: relative risk, WTP: willingness to pay.

It is important to note that the sensitivity profile of the model parameters would change if our inputs for the baseline analysis differed. For example, the sensitivity of NH incidence would be much greater if CGM-reported incidence rates were used, which would make it more sensitive to the value-based price. Likewise, the sensitivity of clinical parameters for IAH and SH would be greater using the higher documented rates.

3.4.3 Scenario analysis

Scenario analysis using CGM-recorded nocturnal hypoglycemia incidence was performed to compare against the base case that uses data from a study using SMBG to monitor glucose levels. The HypoDE study¹³⁵ monitored glucose levels of T1D patients using CGM technologies, and the reported frequency of NH was approximately 5 times more than what was reported using SMBG tests in the

HypoAna study¹¹³. Using the NH incidence derived from the HypoDE study increases the incremental gain in patient outcomes (QALYs) and cost savings by 1.43 (i.e., 3.76 - 2.32) QALYs and \$ 2585.23 (i.e., \$8,576.18 - \$6,170.95) (Table 7). This leads to a value-based price of \$8,582.81, which corresponds to a \$3,213.51 increase from the base case price of \$5,269.30.

Table 7: Point estimates for base case and scenario analysis of value-based price.

	T ₀		T _x		$\Delta (T_x - T_0)$		Headroom (\$)	VBP (\$/year)
	QALY (yrs)	Cost (\$)	QALY (yrs)	Cost (\$)	Δ QALY (yrs)	Δ Cost (\$)		
Base case	9.23	93,437.51	11.54	89,438.32	2.31	-3,999.19	119,728.36	5,179.73
Mean (95% CI)	(8.80, 9.64)	(84,758.00, 108,545.27)	(11.16, 11.90)	(81,083.14, 102,995.68)	(1.99, 2.64)	(-5,744.93, -3,016.23)	(102,569.27, 137,672.81)	(4,437.39, 5,956.05)
CGM-recorded NH incidence								
HypoDE¹³⁵	6.53	107,739.34	10.29	97,181.35	3.76	-10,557.99	198,389.81	8,582.81
HypoAna¹¹³	-1.87	122,886.91	6.34	104,285.56	8.22	-18,601.35	429,493.89	18,580.93
IAH prevalence & SH incidence¹²⁵								
Gold	8.63	110,868.21	11.13	100,306.34	2.51	-10,561.86	135,848.99	5,850.10
Clarke	8.53	108,215.80	11.10	97,642.15	2.56	-10,573.66	138,772.37	6,003.62
Pedersen-Bjergaard	7.39	119,687.01	10.33	104,563.72	2.94	-15,123.28	162,156.05	7,015.26
Productivity costs^{108,121}	9.23	123,800.40	11.55	104,713.99	2.32	-19,086.41	135,223.82	5,850.10

Further scenario analysis considered IAH prevalence diagnosed through different methods derived by Gold¹²², Clarke¹²³, and Pedersen-Bjergaard¹²⁴. There are also corresponding increases in SH incidence for T1D patients with IAH. Lin *et al.*¹²⁵ reported IAH prevalence in a T1D cohort using the Gold, Clarke, and Pedersen-Bjergaard questionnaires, which were 33.3%, 43.7% and 77.0%, respectively. IAH or hypoglycemia unawareness identified by the Gold, Clarke, and Pedersen-Bjergaard method were associated with 6, 4.63 and 5.83-fold increases in risk of severe hypoglycemia, respectively. This led to gains of incremental gains in QALYs and cost-savings between the ranges of 2.51 to 2.94 QALYs and

\$10,561.86 to \$15,123.28, respectively (Table 7). The corresponding value-based price is estimated to be between \$5,850.10 and \$7,015.26, depending on the method used to diagnose IAH.

By including productivity costs for every non-severe daytime or nocturnal hypoglycemic event, the incremental gain from cost-savings grows by \$11,113.66 (i.e., \$19,086.41 - \$7,972.75) from the base case, and increases the value-based price to \$5,850.10 per year (Table 7).

Given the uncertainty in a range of important model inputs, we used conservative estimates for the base case analysis. Therefore, the different scenarios on model inputs pertaining to hypoglycemia incidence, IAH prevalence, and costs, all increase the value-based price of the SSTR2a drug product. Other scenarios pertaining to the model time horizon, would likely increase the value-based price. The model time horizon assumes all patients enter the model 44 years based on the mean age of the patient cohorts in the clinical trials that were used in the model. However, the onset of type 1 diabetes occur before 40 years of age and peaks at around 14 years.^{136,137} This suggests that true time horizon of the drug's cost-effectiveness is longer than 40 years, which would translate to a higher value-based price.

3.5 Discussion

The value-based pricing model can be used as a tool to evaluate a drug candidate in reference to its target product profile and other available evidence found from various sources (e.g., market data, clinical databases). Prices are associated with profits for shareholders, affordability for payers, and accessibility to patients. Given the implications of drug prices across these stakeholders, prices should be set such that the therapy is accessible to patients while satisfying investors' expectations and payers' cost-effectiveness requirements.

The value-based price (VBP) of a SSTR2a drug that reduces severe and non-severe hypoglycemia occurrences by 10% and 30% in the US T1D population, respectively, was estimated to be \$5,179.73 (95 CI \$4,437.39, \$5,956.05) per year. The estimated VBP is 8% higher than the listed wholesale price of Victoza – a comparable therapeutic (GLP-1 agonist that increases endogenous insulin levels) that has an

average wholesale price of \$4774.00 annually¹¹⁹. Victoza's global sales revenue for 2017 was \$3.49 billion USD (23.2 DKK billion)¹³⁸. This suggests a potentially successful drug development campaign.

However, decision-makers must weigh the benefits from sales revenue against the costs and development risks throughout the drug development process. In addition, expectations on revenue, costs and risks are dynamic, which necessitates consideration of decision flexibility in the investment. In order to consider these additional factors, financial valuation via real options analysis can be performed to estimate the FCF from investing in a drug candidate. Using the value-based price for such analysis will assess whether the developing a cost-effective therapy can lead to a positive FCF outcome. This analysis will be performed in the following chapter to complete the VB-ROA framework.

The most sensitive model parameter on the VBP was the payer's willingness to pay (λ) for a gain in QALY. In the US, λ typically ranges from \$50,000 to \$180,000 per QALY. Although there are no approved treatments that specifically prevents hypoglycemia, there are many competing technologies to better control glucose levels, which in turn may reduce the risk of hypoglycemia¹³⁹. This suggests that payers may be more price sensitive in the diabetes space given the high number of comparable treatments they would be able to consider. In order to be conservative, the model used the lower end (\$50,000/QALY) of the WTP range.

Non-severe daytime hypoglycemia was shown to have greatest cumulative disease burden and healthcare costs over the lifetime of the model. On a per event basis, severe hypoglycemia has a greater impact on HRQoL outcomes and is costlier than non-severe events. However, non-severe daytime hypoglycemia occurs 45 and 100 times more frequently than severe hypoglycemia for T1D patients with or without IAH, respectively. Based on base case results, reducing the frequency of non-severe hypoglycemia would be an important outcome to consider in development and commercialization strategies.

Nocturnal hypoglycemia leads to loss in productivity the following day, and poses a greater risk compared to daytime events for IAH and severe hypoglycemia. NH is more burdensome than non-severe daytime events; however, in this analysis, daytime events had a greater impact on the value-based price. This finding was attributed to the greater frequency of daytime events compared to nocturnal. However, the differences in frequency may be attributed to difficulty in measuring glucose levels during sleep. The clinical trials referenced in the model did not use continuous glucose monitoring (CGM) monitors so nocturnal events are likely to have been under reported.

3.5.1 Limitations

There are several limitations to this analysis that potentially underestimates the value-based price. We assumed the average age of T1D patients was 44 years based on the patient cohort characteristics of the HypoAna and BEGIN BB trials that were referenced to populate the clinical model. However, the highest T1D incidence is observed is at 14 years of age^{136,137}, which suggests that the lifetime horizon was underestimated along with the corresponding $\Delta QALY$, $\Delta Cost$, and value-based price.

T1D is a chronic disease that comes with micro- and macrovascular complications that result in considerable morbidity affecting the organ system (e.g., heart, liver, etc.), which can be further exacerbated due to hypoglycemia¹⁴⁰. More complicated state-transition models exist to capture the effects of different co-morbidities (e.g., CORE Diabetes model¹¹⁰). We decided to go forward with the simple model as the objective of this analysis was to estimate the price of an SSTR2a treatment based on its performance on reducing hypoglycemia and its direct impact on costs and patient quality of life.

Hypoglycemia-induced diabetes complications were not considered based on the assumption that co-morbidities would be similar across treatment groups. This assumption underestimates $\Delta Cost$ and $\Delta QALY$ because the model does not consider costs and HRQoL implications associated with any co-morbidities. Mortality rates would increase due to co-morbidities, but the model adjusted mortality by the RR of death for T1D patients compared to the general population.

The impact of SH on the value-based price is likely to have been underestimated. While there is clinical evidence that severe hypoglycemia is associated with worsening long term health outcomes, including increased mortality^{72,74}, these impacts were not considered in this model because it involves other comorbidities that were not modeled. This limits the model from assessing the impact of death from severe hypoglycemia in relation to the gains in QALYs. Also, cost per severe hypoglycemic event was undervalued as it did not consider the expected cost of glucagon treatment, which can be administered as rescue therapy.⁷² Costs pertaining to glucagon treatment in response to severe hypoglycemia was excluded from our analysis as we only considered hypoglycemia requiring medical attention as opposed to needing non-medical assistance.¹¹⁸ This was based on an economic analysis performed by Foos *et al.* (2015)¹¹⁸ where glucagon treatment costs were excluded because the analysis only considered severe hypoglycemia requiring medical attention. Glucagon costs (\$55 per event) were considered when assistance is provided outside of a clinical setting.

Although the model was based on a US population, the RCTs referenced in this analysis were studies that did not include US clinical sites. This is a limitation because the characteristics of different populations (e.g., socioeconomic, age demographic, diet) may impact the frequency of hypoglycemia, insulin requirements, and its response to the novel treatment. The HypoAna trial was based in Denmark, and the BEGIN BB T1 study included clinical sites in the Japan (41%), UK (15%), India (13%), Finland (10%), Italy (10%), Brazil (5%), and Macedonia (6%). We assumed the patient cohort in these studies are comparable to the US population in terms of insulin dose requirements and hypoglycemia rates because the studies were generally based on patient cohorts from developed countries.

The RCTs used in the model relied on SMBG tests and patient diaries or questionnaires to confirm hypoglycemic events, rather than use CGM-based measurements. This leads to variations in reported rates of hypoglycemic events, where CGM-based measurements detect higher occurrence of hypoglycemia. There is a need for studies using CGM technologies to detect hypoglycemia as they

provide more accurate rates of occurrences, especially for nocturnal hypoglycemia. This suggests that using data generated through SMBG test methods underestimates hypoglycemia incidence.

Reported results were sensitive to relative rates of hypoglycemia events, as well as the disutility associated with these events. We relied on results from a short-term (26-week) clinical trial to model long-term effectiveness of the T1D population in the S2 health state.¹¹⁴ The S1 health state was modelled using a longer term study (2-year).^{92,113} Longer-term follow-up studies would be useful in better determining the incidence of non-severe and severe hypoglycemia in T1D patients with and without IAH. Also, data on long-term impact of hypoglycemic events on quality of life, clinical outcomes, and costs need to be better quantified to support the model's long time horizon.

As with any early-stage drug candidate that has yet to conduct clinical trials, there is no evidence regarding real world effectiveness. Assumptions on the SSTR2a's performance were based on clinical experts' views of what constitutes a clinically meaningful difference between new vs standard therapies. We assumed that the target product profile of the SSTR2a would meet the requirements for a clinical meaningful impact on reducing hypoglycemic events. The reduction in relative risk for non-severe daytime hypoglycemia was the same for nocturnal episodes under the assumption that the drug's effect would have equal impact on all non-severe events regardless of time of day. As SSTR2a technologies are developed, and clinical data begins to define the performance of this class of product, the new inputs can be incorporated for analysis and the model will gradually become more accurate.

The value-based pricing model was also sensitive to IAH prevalence as seen through the scenario analysis. We assumed IAH prevalence as static, but it may be dynamic and increase with age, which suggests that our assumptions on IAH underestimates the value-based price. IAH prevalence T1D patients with IAH are unable to detect hypoglycemia as they are desensitized to its symptoms; therefore, the frequency of non-severe episodes that would impact patient quality of life would be less. The model inputs suggest that those with IAH have higher frequencies of all types of hypoglycemia, and each

occurrence has a negative impact on patient HRQoL. One must acknowledge that a non-severe event where no symptoms are detected, due to IAH, would also mean that there would be no impact on patient HRQoL for that occurrence. This means that our model may over-count the number of non-severe hypoglycemic cases that impact patient HRQoL for the T1D cohort with IAH.

Because of the limitations to the model outlined above, a conservative approach to making assumptions was adopted, which likely results in underestimating the true value-based price. However, this decision analytic model was not intended to calculate the exact cost-effective price, nor was it to consider every aspect of the disease with exact precision. Rather, this model simplifies reality such that decision-makers can evaluate the potential value of an early-stage drug candidate. Although an exact estimate is difficult to calculate given that lack of data on important parameters, such as the drug's efficacy, this model can be used to understand the parameters important to the value-based price for this particular drug candidate. Identifying these parameters can help with designing development strategies, and adjusting the TPP parameters or clinical assumptions, that better track the commercial value of the drug candidate while having a greater consideration for cost-effectiveness requirements.

CHAPTER 4. VB-ROA OF A PHASE 1 DRUG CANDIDATE

4.1 Introduction

Hypoglycemia is a contributing factor to poor glucose management and can cause complications and death for people with diabetes. Zucara Therapeutics is a Canadian life sciences company with the objective of developing the first once-daily therapeutic to prevent hypoglycemia in people with diabetes undergoing insulin therapy.¹⁰³

Current available therapies are reactive (e.g., glucagon injections) where patients experiencing hypoglycemia are rescued from the symptoms. As described in Section 3.2.2, the technology regulates a hormone in the pancreas called somatostatin, which is dysregulated in the insulin-dependent diabetes population. Improved regulation of somatostatin brought about through the SSTR2a can function to restore the ability to release more glucose into the bloodstream when levels are low.

Similar to Zucara's therapeutic asset, our case example assumed an SSTR2a that is currently in pre-clinical development and is in preparation for phase 1 clinical trials. However, many of the data inputted into the model were derived from published sources with no affiliation with Zucara Therapeutics. In Chapter 3, we developed a target product profile (TPP) for SSTR2a that reduces non-severe symptomatic and severe hypoglycemic cases by 30% and 10%, respectively, compared to usual care. The TPP (Table 1) was used to perform headroom analysis to estimate a cost-effective price based on the US T1D population and a λ of \$50,000 per QALY. The resulting value-based price for an SSTR2a with the TPP, as shown in Table 1, was \$5,178 (95% CI \$4,437, \$5,956) per year per patient (Figure 14 & Table 5).

Most of the value in early-stage biotech firms can be explained by future expectations on the technologies being developed.^{16,38,58,63} The estimated value-based price can serve as an indicator for future commercial success and be used to support development decisions. However, there are many other variables that are not been considered in headroom analysis that is important for early-stage drug

development decision-making including: development costs, operating costs, probability of development success, along with revenues, market size and growth rates. In order to consider these variables, a real options analysis using the binomial option pricing model (BOPM) was conducted using the value-based price.

The BOPM is well-suited to consider evaluate drug development projects as it is able to consider the decision flexibility inherent in drug development, as well as uncertainty in the market value of the drug.^{16,38,49,58,62,63} The flexibility component of the BOPM assumes that management will only continue investing into development when commercial outcomes look positive. Uncertainty in the market potential of the drug is considered by using a measures of volatility to project a range of upper and lower estimates that are structured into a binomial lattice.

4.2 Study Objective

The objective of this study is to assess the commercial potential of developing an SSTR2a drug candidate based on the estimated annual value-based price of \$5,178 (95% CI \$4,437, \$5,956). To do so, the value-based price will be used to estimate future sales revenues and compare them against corresponding drug development costs and risks through a real options analysis via the BOPM.

4.3 Methods

The second step of the VB-ROA framework involves incorporating the estimated VBP into the binomial option pricing model, which considers the commercial parameters summarized [Table 9](#) and [Table 11](#). First, we estimated the range of market values for the SSTR2a drug candidate (A_t) based the VBP (Section [4.3.1](#)). Second, we price the options (V_t) using the binomial option pricing model that compares the development cost (S_t) against the estimated market values (A_t) adjusted for development risk (θ_t) (Section [4.3.2](#)). Finally, we performed a one-way sensitivity analysis to identify model parameters that were most sensitive to option value.

4.3.1 Market value of the SSTR2a drug candidate

The drug candidate's market value (A_t) is the net present value of projected yearly free cash flows (FCFs) by subtracting future revenues from costs (Equation 8). Sales revenues and operating costs were projected until patent expiry^{16,38}, which was assumed to be 10 years. The patenting process for drug development typically begins at the pre-clinical phase, and once approved, is granted market exclusivity for 20 years. Since it takes about 10 years to develop a drug from the pre-clinical stage, we assumed that there were only 10 years of patent life remaining once the drug launches.

Operating costs are day-to-day expenses related to business operations, which included manufacturing (COGS), sales & distribution, and general administrative expenses (Table 8). The 2018 US tax rate of 21%¹⁴¹ was applied to estimate after-tax operating profits. Development costs (i.e., capital expenditures, S_t) were not considered when estimating the market value of the underlying technology as these costs are built into the model when pricing the options. We assumed the development cost estimates were adjusted for tax shields.

Operating costs were set based on % of revenue calculated from historical financial statements from a comparable company in the diabetes space: Novo Nordisk – a large pharmaceutical company with 80% of their revenues generated through their products in diabetes care (Table 9).¹³⁸ Although not considered an early-stage company, the operating costs are effective once the drug has been approved and launched, which can be comparable to more established firms.

Table 8: Breakdown of variables to calculate asset value.

Variables	Source and/or description of variables
A	Asset value – i.e., profit generated after bringing the drug candidate to market
r_c	Investors' cost of capital – typically around 15% for early-stage drug development projects
Profit	Equals revenue, less operating costs and tax
Operating Cost	Includes cost of goods sold (COGS), sales and distribution costs, general and administration expenses (G&A)
Revenue	Price \times quantity sold
Quantity	Market size \times penetration rate (%) \times market growth rate
Market size	Estimated using disease prevalence data
Penetration rate	Estimated from market data from industry grey literature
Market growth rate	Estimated using disease incidence data, or industry grey literature
Terminal growth rate	Estimated from market data from industry grey literature

Revenues were estimated by multiplying the quantity of units sold with the price per unit (Table 8). The quantity of units sold requires estimations on market size and penetration rates. A T1D prevalence estimate of 1.3 million based on published data was applied to project the market size for the drug.^{68–70} Of the entire T1D population in the US, we assumed those who have recently encountered nocturnal hypoglycemia would be in the market for the treatment, which was approximately 40%.⁸³ The growth in market size was assumed to be 5.2% per year based on forecasts estimated by GlobalData¹⁴² using published prevalence⁶⁸ and incidence data⁸³.

Revenues were expected to change with time, where sales typically grow until it reaches its peak rate, and then decrease once the patent expires.^{16,38} To date, there is no therapeutic drug that prevents hypoglycemia, which means that the SSTR2a would be a first-in-class prophylactic therapy to specifically for hypoglycemia as an indication. Therefore, the peak market penetration rate was set based on historical sales performance for other first-in-class drugs, which was estimated to be 40%.²¹ To simplify the analysis, we assumed initial market penetration rate of 1% with straight-line growth to peak market capture over a 10-year timespan. An empirical study by Bauer and Fischer (2000)¹⁴³ has shown that the

time to peak sales for first-in-class drugs range between 8 to 10 years. After 10 years from launch, we assumed patent expiry and set a terminal growth rate of -3% based on estimates for biologics drugs enteric generic competition.¹⁴⁴

Table 9: Summary of commercial parameter inputs for the binomial option pricing method.
T1D: type 1 diabetes, NH: nocturnal hypoglycemia.

Commercial Parameters	Mean (95% CI)	Source
<u>Profits (A_t)</u>		
<i>Revenues</i>		
Price (per patient per year)	\$5,179.73 (\$4,437.39, \$5,956.05)	Table 5
Market Size		
T1D prevalence	1.3 MM	68
Proportion (%) with NH	40% (39.4%, 41.7%)	83
T1D incidence (%)	5.2%	142
Terminal growth (%)	-3.0%	144
Market Penetration Rate		
Initial rate (%)	1%	N/A
Peak rate (%)	40% (1 st to market)	21
<i>Costs</i>		
Operating costs <i>Mean (SE)</i>		
Cost of goods sold (COGS)	15.9% (0.8%)	138
Sales & Distribution	26.2% (1.1%)	138
General Administration (G&A)	3.7% (0.3%)	138
<u>Other rates</u>		
Discount rate (r_d)	13.2% (10.3%, 16.1%)	145
Tax rate	21%	145

N/A: not available due to lack of data.

The binomial structure follows 1-year time intervals, and all annual cash flow projections were discounted using a 13.2% cost-of-capital (i.e., discount rate for the asset value). The referenced cost-of-capital was derived using financial data of small biotechnology firms from 2006 to 2008 and estimated by

Harrington (2012) using the capital asset pricing model (CAPM) framework.¹⁴⁵ The cash flows are discounted to the initial decision node at t_0 .

Table 10: Binomial option pricing method input parameters for asset values ($A_{t,k}$). u: upward adjustment factor, d: downward adjustment factor, p: risk-neutral probability.

BOPM Parameters	Input Values
Project volatility (σ)	26%
u	1.30
d	0.77
p (risk-neutral probability)	53%

The estimated $A_{0,1}$ was used to populate the possible market value scenarios of the underlying drug candidate based on a σ of 26%, which was estimated by computing the log-normal annual stock returns of the selected comparable company (Novo Nordisk) from 1981 to 2018.¹⁴⁶ The volatility estimate translates to annual upside and downside adjustments to market value of 130% and 77%, respectively (Table 10). The market value at t_0 is then adjusted using the upward weight to estimate for $A_{1,1}$ and the downward weight to estimate $A_{2,2}$. This process is repeated for each scenario (k) until the terminal timepoint (Year 7).

4.3.2 Calculating option value

To solve for option value (V_t) at a particular decision node, the estimated market value (A_t) of the drug candidate was adjusted by the corresponding probability of passing the development stage (θ_t), and then subtracted by the capital expenditures (S_t) required to finance it (Equation 7). Options are contingent upon passing the prior development stage, therefore, the option value is adjusted for development risk. The terminal options (V_7) were first calculated using the terminal market values (A_7) as described in Equation 10. If the calculation leads to a negative value, then the option is not exercised and is valued at \$0. If the calculation is positive, then the option is exercised and its value is the difference between the

risk-adjusted market value of the underlying technology and the cost to finance the next development phase (i.e., $A_7\theta_7 - S_7$).

Table 11: Drug development parameters for BOPM. NDA: new drug application, BLA: biological license application.

Development Parameters	Length (t)	Probability of Success (θ_t)	Capital Expenditures (S_t)	Source
Phase 1	1 year	63.2%	\$27.93 (\$3.31)	13,52,53
Phase 2	2 years	29.0%	\$64.70 (\$7.29)	13,52,53
Phase 3	3 years	56%	\$281.98 (\$37.65)	13,52,53
NDA/BLA	1 year	72.7%	\$2.4	52,53,147
Product Launch	1 year	100%	\$94.3 (\$63.5, \$125.1)	148

The drug development parameters used to calculate option value are shown in [Table 11](#). Clinical development costs were estimated in reference to DiMasi *et al.* (2016)¹³ and adjusted to 2018 terms using a 2% inflation rate. The average duration of each phase was taken from data published by Llano *et al.* (2016).⁵² The cost to submit an NDA was taken from information published by the US FDA.¹⁴⁷ Drug product launch costs were taken from a published grey literature.¹⁴⁸ Risks associated with clinical development are considered by including probability of clinical trial success published by Hay et al (2014).⁵³

Once the terminal options are calculated, all preceding options are solved recursively using a risk-free probability of 53% based on a risk-free rate of 5% according to [Equation 11](#). All options were discounted using the risk-free rate of 5%.

4.3.3 Sensitivity analysis

One-way sensitivity analysis on the option value for phase 1 development ($V_{0,1}$) was performed by adjusting VB-ROA model input parameters by $\pm 50\%$. To determine the impact of drug development parameters with respect to option value, we assessed estimates on capital expenditures (i.e., clinical development costs, NDA and market launch costs) and probabilities of development success. Sensitivity

to commercial inputs were assessed by modulating model parameters pertaining to operating costs (i.e., COGS, G&A, Sales and distribution), revenues (i.e., drug price, T1D prevalence and incidence, terminal growth rate, market penetration rate, % with recent NH), volatility (σ) of the underlying asset, and the cost-of-capital. Finally, the sensitivity of cost-effectiveness parameters to option value was assessed by evaluating clinical parameters (HRQoL, hypoglycemia incidence, treatment effect), cost parameters (i.e., hypoglycemia management costs), and the discount rate to adjust costs and QALYs into present value terms.

4.4 Results

4.4.1 Base case

The estimated mean (95% CI) market value of the drug candidate at the initial decision node to invest in phase 1 clinical trials was \$1,396.90 Million (MM), which was derived using the inputs summarized from [Table 9](#) to [Table 11](#). After the successful completion of phase 1 trials, the corresponding market value of the drug candidate has an upper and lower estimate of \$1,073.75 MM ($A_{1,2}$) and \$1,817.31 MM ($A_{1,1}$), respectively. After phase 2 trials, the market value is estimated to range from \$634.42 MM ($A_{3,4}$) to \$3,075.77 MM ($A_{3,1}$). If we assume development continues until it reaches the launch phase, the market value of the SSTR2a drug candidate will reach anywhere between \$227.47 MM ($A_{7,8}$) to \$8,716.31 MM ($A_{7,1}$).

Real option values at different decision nodes throughout the development process are reported in the bottom of [Figure 17](#). The option value to invest in phase 1 development was estimated to be \$0 ($V_{0,1}$) based on the development cost of \$27.93 MM and the risk-adjusted option value at $t=1$ being either \$0 MM ($V_{1,2}$) or \$67.32 MM ($V_{1,1}$). This suggests that if phase 1 development is funded and trial results successfully pass, the option on the drug candidate to undergo phase 2 development can be valued at either \$0 MM ($V_{1,2}$) or \$67.32 MM ($V_{1,1}$).

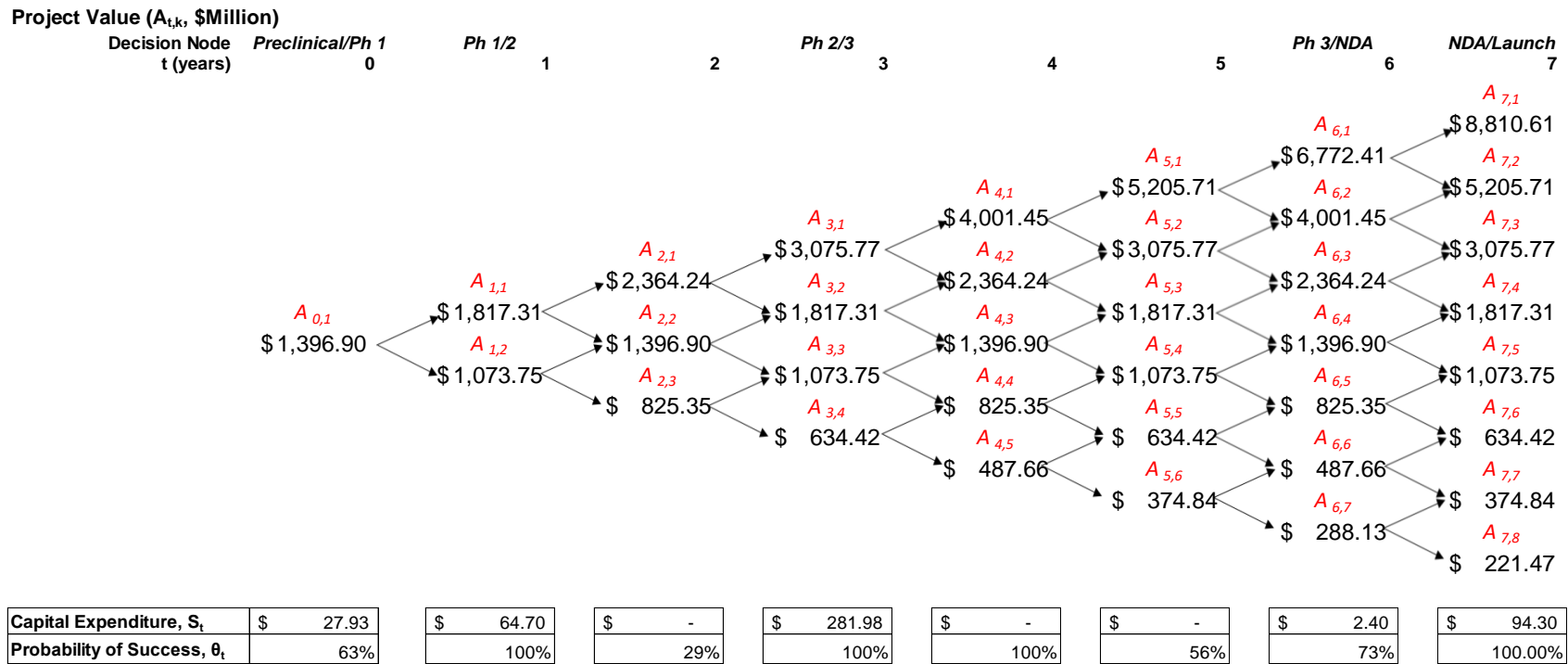


Figure 16: Distribution in the market value of the drug candidate ($A_{t,k}$) over the development time horizon (yr 7).

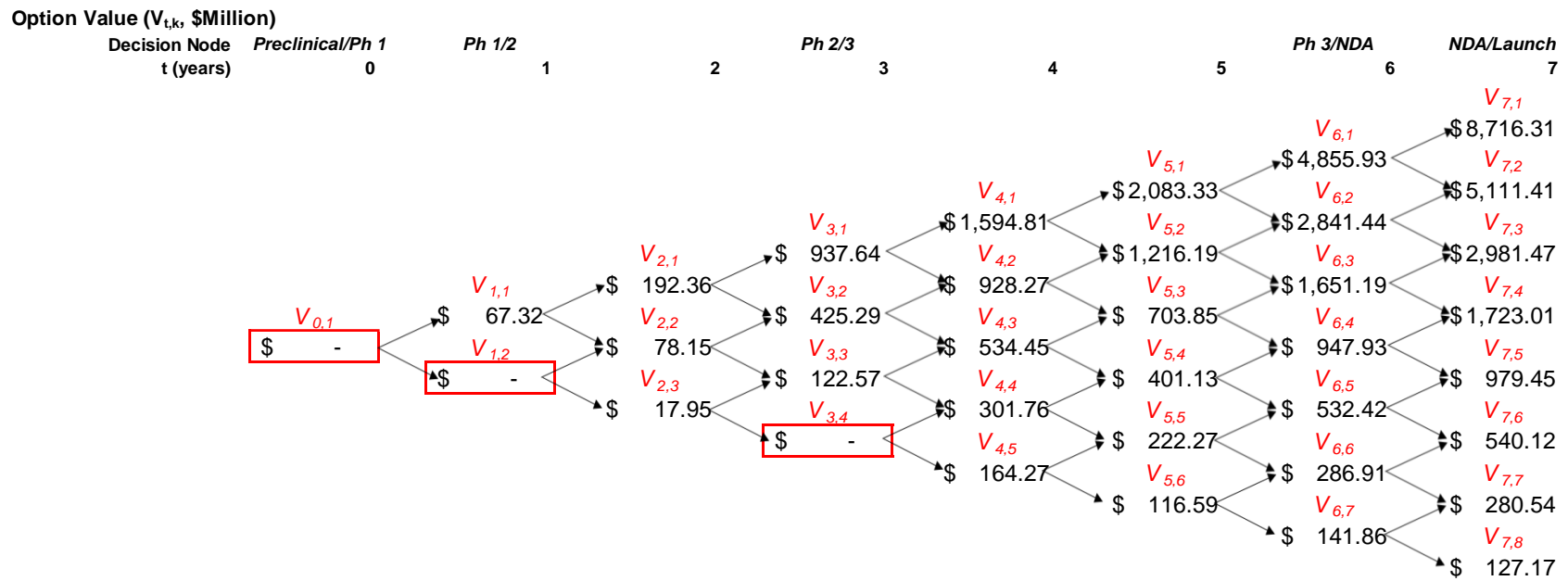


Figure 17: Real option values ($V_{t,k}$) after adjusting for clinical development risks ($\theta_{t,k}$).

The two possible option values prior to the decision to launch phase 2 trials is based on the estimated value of future options at $t=3$ along with the cost and probability of passing phase 2 clinical trials. If the drug candidate passes through phase 2 trials, the option value to invest in phase 3 trials ranges from \$0 MM ($V_{3,4}$) to \$937.64 MM ($V_{3,1}$). Since the option values prior to the successful completion of phase 3 trials can be \$0, management needs to carefully evaluate their options to ensure a positive financial return.

Options valued at \$0 indicate that the costs to fund the respective stages in development are greater than the risk-adjusted financial benefits from commercializing the drug candidate. The decision flexibility in option valuation limits the downside to \$0 and prevents negative investment returns from occurring. The value in decision flexibility is dependent on management behaving rationally, which is to forgo financing development when evidence suggests the commercial potential of the drug candidate does not appear to outweigh the immediate cost of development.

Option values after the drug candidate passes phase 3 trials (i.e., V_4 to V_6) are estimated to always be positive. This is because much of the development risk has passed and the remaining cost to complete development are marginal compared to earlier phases. Upon successful phase 3 trials, the option value to apply for a new drug application (NDA) ranges from \$141.63 MM ($V_{6,7}$) to \$4,855.93 MM ($V_{6,1}$). Similarly, the option value to proceed toward product launch is projected to generate a positive financial return that ranges from \$127.17 MM ($V_{7,8}$) to \$8,716.31 MM ($V_{7,1}$). This indicates that options available after successfully passing phase 3 clinical trials should always be exercised.

4.4.2 One-way sensitivity analysis

One-way sensitivity analysis on the option value for phase 1 development ($V_{0,1}$) is summarized in [Figure 18](#). In general, ‘Commercial & Epidemiological’ model inputs were most sensitive to option value ($V_{t,k}$) with the cost of capital (r_c) for the investment having the greatest effect. Aside from cost of capital, model parameters directly involved in calculating revenues [e.g., ‘Drug Price’, ‘T1D Prevalence’, ‘Recent

NH (%)'] had equal effects on option value. The option value is also sensitive to peak market share and T1D incidence because revenue calculations consider the growth in patient population, as well as, changes in market share where we assume straight-line growth. In terms of operating costs, manufacturing costs (COGS) and 'Sales and Distribution' costs were also shown to influence option value. The volatility (σ) of the underlying asset was found to not be sensitive to option value relative to other commercial parameters.

Model parameters for clinical development were found to influence option value. Probabilities around successfully completing phase 3 trials (θ_6) and receiving regulatory approval upon NDA submission (θ_7) exhibited greater sensitivity to option value compared to success rates for earlier development stages (i.e., θ_0 to θ_5). For development costs (i.e., capital expenditures), clinical trial costs were more sensitive to option value than development costs after market approval. Relative to clinical development risks, inputs pertaining to development costs were less sensitive to option value. A further discussion on non-profit funding mechanisms to advance early-stage drug candidates is described in [Section 4.5](#).

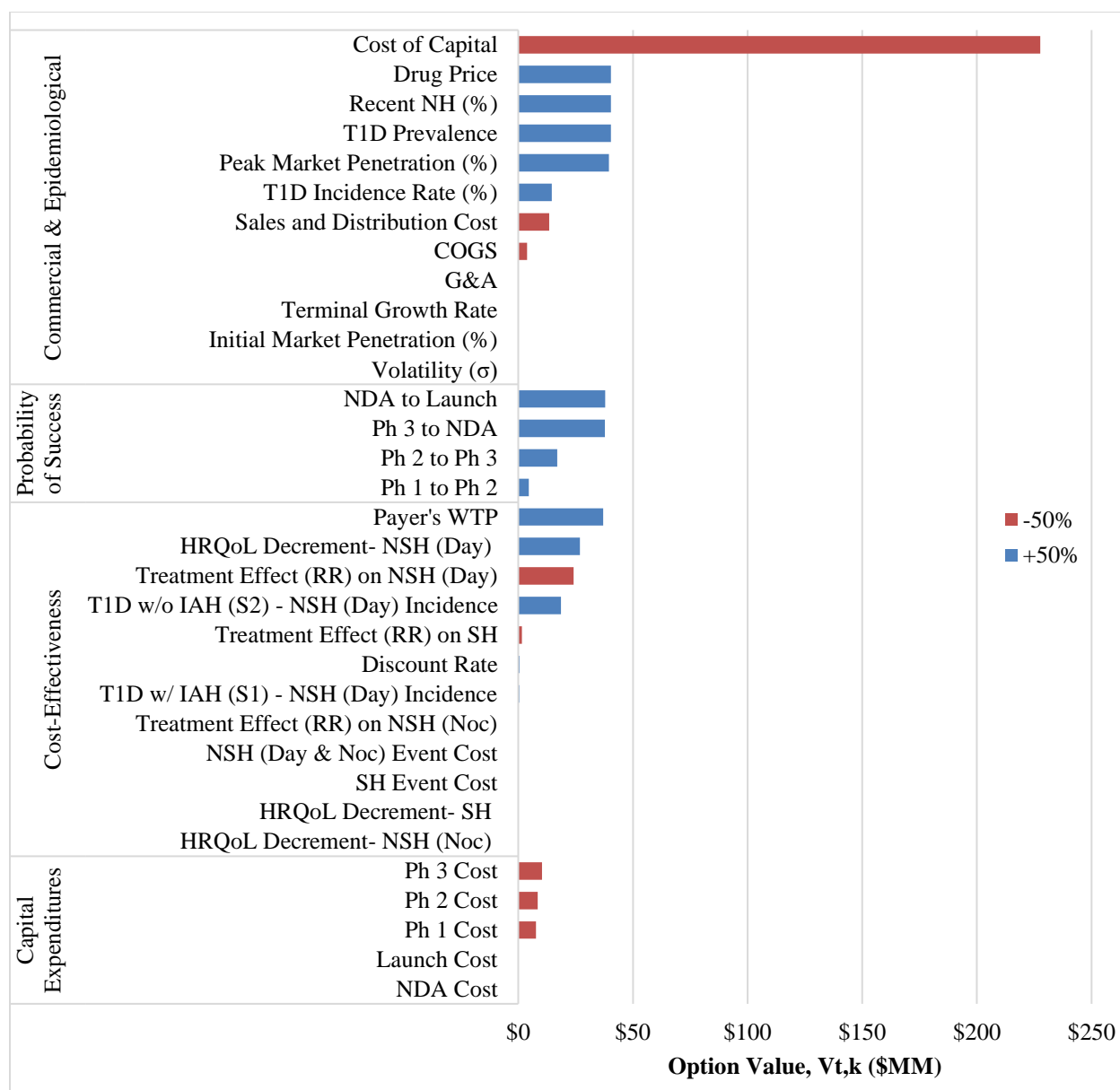


Figure 18: One-way sensitivity analysis results on the VB-ROA of an SSSTR2a drug candidate.
T1D: type 1 diabetes, COGS: cost of goods sold (manufacturing costs), G&A: general and administrative costs, NDA: new drug application, WTP: willingness to pay, RR: relative rate, NSH: non-severe hypoglycemia, Noc: nocturnal, SH: severe hypoglycemia, NH: Nocturnal hypoglycemia, HRQoL: health-related quality of life, Ph: phase, IAH: impaired awareness of hypoglycemia, NDA: new drug application, σ : asset value volatility.

Five cost-effectiveness parameters used to estimate the value-based drug price were sensitive to the option value to invest in phase 1 development (Figure 18). Payers' λ exhibited the greatest sensitivity. In general, cost-effectiveness parameters associated with non-severe hypoglycemia [i.e., HRQoL weights,

event rates, relative risk (RR) of events of the reference drug] exhibited greater sensitivity than inputs related to severe hypoglycemia. Of all the levels of hypoglycemia, the event rates for non-severe daytime hypoglycemia for T1D patients with IAH were the only parameters sensitive to option value.

4.5 Discussion

We assume that decisions to continue or halt development will be during times when new evidence has been generated from the completion of clinical trials. Although options were valued every year in the development process, the value of the initial option ($V_{0,1}$) is the primary result that management should consider supporting the decision to invest in phase 1 trials for the SSTR2a drug candidate. The option to fund phase 1 clinical development ($V_{0,1}$) using the VB-ROA framework indicates that the drug candidate is unlikely to generate a net positive investment return due to the high level of unresolved development risks. As a result, management would likely forgo investment, which results in a net \$0 option value.

Phase 1 drug candidates may be too early in the development process for profit-seeking investors to fully absorb the development risks and costs. The option value for the phase 1 drug candidate was derived recursively from option values in the future. This implies that future option values can be realized if the drug candidate progresses through the development process. Although the scenario evaluated is not profitable prior to entering phase 2, future options (V_1 to V_7) in which $V_{0,1}$ is based upon can be positive. This suggests that there is the potential for the drug candidate, as defined, to become commercially viable investment in the future. Also, the development strategy can be refined (i.e. focusing the TPP and other model inputs that can be controlled by the developer or funder), which could produce a more profitable option value for Phase 1 development. Once the drug candidate passes phase 3 development, the corresponding future option values are estimated to always generate a positive FCF outcome for investors.

To address funding gaps to commercialize early-stage biomedical technologies, private-public partnerships have been established to function as a catalyst to de-risk at the earliest stages in development.^{35–37,149} It is important to note that investment decisions made by public funders (e.g., government, charity funds) are not necessarily profit-driven. Some of these funders may be driven by philanthropic, social, or policy motives. Under this different framework, public funds may fund drug development initiatives that are unlikely to generate a profit given the risks and costs involved. This is a common occurrence for the funding of very early stage (discovery) health research which is in large part funded by national government granting agencies (e.g. CIHR, NIH). Other non-profit funders may still consider profitability of opportunities for investment; however, their requirements for returns may be different, which could reflect a difference in cost of capital from these sources. Funding from these sources may be combined into partnerships with for-profit investors.

In fact, the potential for non-profit investors to participate in development of medications for Type 1 diabetes patients is evidenced by the presence of groups such as the Juvenile Diabetes Research Foundation (JDRF) and The Helmsley Charitable Trust who are active in supporting research to improve the health of these individuals. As an example, Zucara Therapeutics¹⁵⁰ has developed their preclinical SSTR2a drug candidate with investment from a group of not-for-profit funders (The Helmsley Charitable Trust¹⁵¹, Juvenile Diabetes Research Fund (JDRF)¹⁵², MaRS Innovation¹⁵³, adMare Bioinnovations¹⁵⁴, and accel-rx). Each of these funding sources has investment motives that not only consider the value of opportunities but also reflects the mandate of their organization. For example, the JDRF's mandate is focused on advancing ways to better treat and prevent T1D.¹⁵² The Helmsely Charitable Trust aims to improve lives by supporting broad health-based initiatives including T1D.¹⁵¹ Organizations like adMare Bioinnovations¹⁵⁴, MaRS Innovation¹⁵³, and Accel-Rx¹⁵⁵, have a mandate to promote economic growth and advance health by enabling the development of early-stage health science technologies.

4.5.1 Limitations

There are limitations to this model that underestimate the real option value to develop the phase 1 SSTR2a drug candidate. The VB-ROA model considers a broad range of inputs spanning epidemiological, clinical, regulatory, and market data. For early-stage technologies, empirical data for many of these inputs are limited, therefore, conservative assumptions were made where necessary.

The market value of the phase 1 drug candidate may have been underestimated due to conservative assumptions made for corresponding model inputs. The model assumed the market share began at 1% and increased in a straight-line manner until it reaches its peak. Financial valuation estimates for early-stage drugs are sensitive to the projected time to reach peak sales because revenues are discounted to account for ‘time value of money’. A recent empirical study on the time to peak sales for pharmaceutical drugs suggest that the timeline has shortened from 8 to 10 years to 5 to 6 years, which suggests that the market value of the underlying drug candidate may have been undervalued. A 5 year time to peak sales would have a corresponding option value for phase 1 development to be at \$16 MM, which supports the decision to invest in the technology.

Parameters pertaining to clinical development (i.e., length of phases, costs and risks) were taken from empirical studies examining the pharmaceutical industry as a whole, which may not reflect the true timelines, costs, and uncertainties pertaining to commercializing an SSTR2a treatment for hypoglycemia. However, these inputs are unique and should be estimated by management based on the clinical development plan. The market value of the drug candidate ($A_{t,k}$) may have been underestimated based on the inputs used pertaining to revenues. The uncertainty in the drug price was discussed previously in [Chapter 3](#). The market size was calculated under the assumption that the target population were US-based T1D patients who have had a recent nocturnal hypoglycemia incident.

The study considered only the cohort experiencing nocturnal hypoglycemia, as this approach is at least initially validated by a company (Zucara) developing a SSTR2a technology for this market

segment.¹⁵⁶ However, this does not mean the SSTR2a treatment will only be sought after by patients experiencing nocturnal hypoglycemia, and the market could be expanded to T1D patients who require improved management of hypoglycemia during the day. Furthermore, the size of the market only considers T1D patients, but if the SSTR2a therapy could benefit all insulin-dependent diabetics at risk for hypoglycemia (including a portion of the T2D population), this scenario, with significantly larger market size, could create a positive option value for development. This is an example of how this model can be used to test a set of inputs (including TPP) to assess the merits of one strategy or another in developing a given technology, in this case SSTR2a.

Although there are uncertainties within the VB-ROA model that limit its accuracy, the analysis enables decision-makers to understand the importance of certain parameters at dictating the commercial value of the drug development project. Parameters that were identified as sensitive to option value can then be prioritized to enable commercialization strategies that enable efficiencies in drug development.

CHAPTER 5. IMPLICATIONS AND CONCLUSIONS

The VB-ROA framework supports a collective decision-making approach to enable the development of cost-effective therapies that meets payer requirements for cost-effectiveness, as well as profitability requirements for drug manufacturers. Real options analysis considers the trade-off between immediate investments needed against the future financial profits generated, along with risks inherent in the drug development process. We ensure the financial benefits are constrained within payer requirements for cost-effectiveness by applying the value-based price when projecting future profits from drug commercialization. The VB-ROA framework considers the risks associated with drug development by adjusting the projected profits by the probability of passing each development phase.

5.1 Sensitivity analysis on VB-ROA to construct development strategies to ‘fail faster’

Performing sensitivity analysis on the VB-ROA framework not only assesses uncertainty around the development decision, but also identifies key parameters with the greatest impact on overall FCF of drug development projects. By identifying these parameters, decision-makers can prioritize development efforts and focus on generating evidence on the most sensitive parameters. This enables development strategies that can quickly validate drug candidates for commercial and economic viability, and further the effort to fail fast and limit lost resources to unsuccessful drug development projects.

In this case analysis, the VB-ROA model results identifies that parameters associated with patient quality of life (e.g., HRQoL weights, adverse event rates) and payer’s WTP for health outcomes were just as important (if not more) to option value than clinical development parameters. This suggests that early-stage development efforts need to include reimbursement considerations. Also, the analysis suggests that reducing adverse events that are non-severe is more important to option value than severe events. This is due to the fact that non-severe events occur much more frequently to a greater proportion of T1D patients than severe events. Therefore, clinical development efforts should aim to maximize the reduction of non-severe hypoglycemia.

5.2 The need for risk-sharing drug development partnerships

The occurrence of financially worthless options (i.e., valued at \$0) for early-stage drug candidates is primarily due to investors' cost-of-capital. Drug manufacturers can increase the final drug price above its value-based price in order to generate a profit (i.e., positive FCF). This reflects the difficulty in relying solely on for-profit drug manufacturers to commercialize novel drugs that are cost-effective. This also highlights the need for drug manufacturers to collaborate with non-profit entities (e.g., government or charitable funds) to share the risks in bringing novel and cost-effective drugs to market.^{35–37}

The SSTR2a drug candidate may not generate a positive value prior to starting phase 1 development, but it may generate a positive option value from phase 2 onward. Drug manufacturers should not be expected to finance projects that are not going to generate profits since their primary aim is to increase shareholder value. Non-profit organizations have mandates that are not geared towards profits. While their investment principles may include an assessment of an opportunity's profitability, it must also be evaluated in its ability to fulfill the mandate, be it for example improving the quality of life of patients suffering from diseases with no available therapies, or other public policy-related outcomes.

Furthermore, a not-for-profit investor may have quite different requirements for return, demands for cost of capital and timelines for investment such that modeled VB-ROA outcomes for these investors could be different than those for for-profit drug manufacturers, for a given investment opportunity. For-profit companies and not-for profit investors must establish effective partnerships to enable funding of technology development from both sides at the appropriate stages of development. Investment agreements could include future provisions to limit drug prices to cost-effective levels if the drug candidate is successfully brought to market.

5.3 Further applications of the VB-ROA framework

The VB-ROA framework was applied as a tool to inform commercial decision-making (i.e., for-profit drug development). However, the model can also be used to inform payer decisions concerning reimbursement. A standardized decision framework that is validated by both the industry and payer communities can enable more effective negotiations between the two parties and develop fair outcome-based agreements. Collective frameworks, such as the VB-ROA, can be used as a tool to better enable collaborations between industry and payers earlier in the product development cycle. By doing so, the drug commercialization process can involve an earlier dialogue with payers where information can be communicated in a manner that better explains its implication across both stakeholders.

5.4 Limitations to the VB-ROA framework

The main limitation in the VB-ROA framework is in its inherent complexity, which may limit its adoption by decision-makers, as it appears to be a ‘black box’. However, one should acknowledge that drug development is a complicated process with many important considerations that warrants the need of subject matter experts in a variety of fields. Currently, the development process considers these variables separately as it moves along each stage, which has led to inefficiencies in resource spending. This has led to the development of novel drugs that are unaffordable to patients, or late-stage drug candidates that are not commercialized because of economic viability. In order to address these inefficiencies, decision-makers must aim to comprehensively understand all variables pertinent to the development of cost-effective therapies.

Another limitation to the model is the vast amount of evidence needed to conduct the VB-ROA. Many of the required inputs do not exist for early-stage drug candidates, such as inputs associated with clinical efficacy. That is not to say that decision-makers do not consider these variables when investing in early-stage drug candidates because the evidence is not available. Decision-makers make assumptions on

what level of clinical effectiveness is needed in order for the drug to address an unmet medical need. For many of these inputs, careful assumptions need to be made in order for the model to be valid and reliable.

5.5 Conclusions

The healthcare sector is unique in that there is a wealth of peer-reviewed literature to support industry, medical, and policy decisions. However, this, coupled with long and expensive development pathways for drug development, with significant risk, makes it difficult for decision-makers to consider the vast amount of information as they evaluate their options. Traditionally, decision-makers from different backgrounds (e.g., clinical, regulatory, commercial) work in a segmented manner that may lead to drug development inefficiencies.

The VB-ROA framework enables decision-makers to consider the vast variety of information spanning different areas of research (clinical, epidemiological, financial, and business) into a single decision model. By doing so, the analysis can assess risks associated with market approval as well as market access.

The VB-ROA framework has suggested that drug manufacturers should not proceed in the development of the phase 1 candidate, as defined, to prevent hypoglycemia for T1D in the US. However, the model also shows that the drug can be valuable to drug manufacturers in the future once it has been further de-risked. The model can also be used to inform development strategy, in that a range of input values may be evaluated. This could inform refinement of the product's TPP or development path to forge an opportunity that would attract investment even in the early stage. Use of this model, or refinement of this model, can be used to inform both investment decisions, but also the framing of the investment opportunity itself, ideally improving the quality of both the technology and the investment.

Collaboration and funding from partnerships of for-profit and not-for-profit investors are needed to bring early-stage technologies to market in a cost-effective manner. Strategies and tools such as the VB-ROA framework to enable these partnerships should be investigated. Further research is also needed

to identify partnership agreements between the pharmaceutical industry and payers to further advance the development of cost-effective and novel therapies.

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