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Assessing the Value of Bimekizumab for TNF-α Inhibitor-Experienced Patients with Psoriatic Arthritis: A Cost-Effectiveness Approach

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ABSTRACT

This thesis intends to analyze the cost-effectiveness of bimekizumab (BKZ) against competing disease-modifying antirheumatic drugs (DMARDs) for psoriatic arthritis (PsA) from the United States healthcare sector perspective. Modeled after Swedish research published by Sigurdardottir et al. (2023), this thesis constructs a Markov model to simulate the clinical pathway of tumor necrosis factor alpha experienced (TNF-α exp) patients over a lifetime horizon of 50 years. The model incorporates treatment response as measured by American College of Rheumatology 50% (ACR50) for joints and Psoriasis Area and Severity Index ##% (PASI##) for skin in addition to changes in the Health Assessment Questionnaire Disability Index (HAQ-DI) score of overall health. Patients remain on treatment by achieving ACR50 and at least PASI75 and will return to best supportive care of concomitant methotrexate if failing to meet these thresholds. Efficacy parameters were derived from Sigurdardottir et al. (2023) stemming from the bimekizumab clinical trial "BE COMPLETE" (Merola et al., 2023) and a network meta-analysis of comparators (Mease et al., 2024). Drug costs and healthcare resource use were derived from the Department of Veterans' Affairs Federal Supply Schedule (FSS), Centers for Medicare and Medicaid (CMS) Part B claims data, and indirect HAQ-DI costs modeled after Ogdie et al. (2022). An opportunity cost of $100,000 per QALY (Vanness et al., 2023) was used as the base case threshold of willingness-to-pay, and $200,000 per quality-adjusted life year (QALY) was applied as a sensitivity analysis. Bimekizumab was not on the cost-effectiveness frontier as it was extended dominated – more costly and less effective than a convex combination of treatments using certolizumab pegol and upadacitinib. From the FSS, the average BKZ contract price per pack (2 doses) is $10,779.02. At the $100,000/QALY ICER threshold, the contract price should be nearly halved to $5,872.87. This model makes strong assumptions regarding the clinical pathway of patients which limits the reliability of this analysis; however, it reflects a key perspective outlined by the Institute for Clinical and Economic Review (ICER) on the Inflation Reduction Act CMS Medicare drug price negotiation process.

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Chapter 1

Introduction

Psoriatic arthritis (PsA) is a chronic, inflammatory joint disease that affects 0.1-1% of the general population but affects ~20% of patients with psoriasis (Karmacharya et al., 2021). PsA ranges in severity and can lead to serious joint damage and disability when not treated effectively. Common symptoms of PsA include fatigue, tendon/joint/extremity inflammation, and reduced motion and stiffness (National Psoriasis Foundation). As of 2005, PsA affects "an estimated 520,000 patients in the U.S. population, and many rate it as a large problem in everyday life" (Gelfand et al., 2005). While not explicitly sequential or linked, PsA and psoriasis frequently overlap in patients; however, "there is little connection between psoriasis severity and PsA severity (National Psoriasis Foundation). There is no definitive diagnostic test for PsA, but diagnosis often stems from symptoms and general diagnostic tests such as ultrasound, MRI, or CT.

Treatments for PsA vary by severity of the disease and by patient symptoms. Generally, there are three treatment approaches for mild, moderate, and severe PsA. Mild flares are often managed with nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroid shots in specific joints (American College of Rheumatology). Moderate PsA or nonresponse to NSAIDs will likely warrant disease-modifying anti-rheumatic drugs (DMARDs) and severe PsA may require biologics or oral medications (American College of Rheumatology). Prescriptions vary based on healthcare systems around the world and regional approvals. The focus of this thesis, bimekizumab, is a biologic "monoclonal IgG1 antibody that selectively inhibits interleukin (IL)-17F and IL-17A" (Merola et al., 2023). It works to suppress various aspects of the immune system to control skin and joint elements of psoriatic arthritis as a result of the immune system attacking the body. It is currently undergoing Phase 3 clinical trials for moderate-to-severe psoriatic arthritis indication after FDA approval for plaque psoriasis use in 2023. Newly released

phase 3 clinical trial data for its efficacy on humans is key to include in a cost-effectiveness model compared to other similar interventions available for treatment.

Value-based pricing, a method of pricing pharmaceutical interventions based on the therapeutic benefit and cost, has historically played a more influential role in healthcare systems outside of the U.S. such as the National Institute for Health and Care Excellence (NICE) in the United Kingdom, the Canadian Agency for Drugs and Technologies in Health (CADTH) in Canada, and the Institute for Quality and Efficiency in Health Care (IQWiG) in Germany. ICER, the Institute for Clinical and Economic Review, plays a similar role in the United States but as a nonfederal agency and watchdog rather than a more influential position. The organization has been creatively deemed “the mouse that roared” because of its strengthening influence (Saltzman, 2019). These organizations are health technology assessment (HTA) organizations that share common goals and values when analyzing clinical data and computing economic evaluations of health interventions.

Cost-effectiveness analyses, comparing a ratio of costs to health benefits, are used to evaluate different treatments and broader economic impacts of interventions. Cost-effectiveness analysis (CEA) organizations outside of the U.S. have historically been more influential role in policy and price guidance than ICER’s more removed role as watchdog. However, ICER is gaining stronger influence in the U.S. through the Inflation Reduction Act’s Medicare price negotiation provision to find value-based prices that can serve as the starting point for negotiations with pharmaceutical companies. ICER’s approach has previously been used in Massachusetts and New York state Medicare program price negotiations but could be nearing a nationwide implementation in the future. With recent evaluations of anticoagulant drugs Eliquis and Xarelto in the first round of CMS drug price negotiation in 2024, ICER published a special report as part of the public comment process but is looking for further guidance from CMS (ICER, 2023) (Liu, 2024).

This thesis intends to analyze the impact of new clinical efficacy data on the value-based price and cost-effectiveness of bimekizumab to treat PsA in tumor necrosis factor-experienced (TNFi-exp)

patients. By evaluating the theory behind CEA and its uses globally, it highlights a gap in the literature concerning the release of new efficacy data. The thesis uses a comprehensive literature review to build the foundation of recently published cost-effectiveness studies for bimekizumab and comparator drugs. Building on a Swedish cost-effectiveness analysis of bimekizumab (Sigurdardottir et al., 2023), this work maintains key assumptions of this model and adjusts it for the United States healthcare perspective. The model incorporates data from new clinical trials, published network meta-analyses, and Medicare reimbursement data to determine the incremental cost-effectiveness ratio (ICER) of bimekizumab relative to comparators and attempt to determine a value-based price based on established thresholds. Ultimately, this thesis serves to assess how ongoing changes in the Medicare drug pricing system, as dictated by the Inflation Reduction Act, could be used to determine a value-based price for a novel therapeutic, providing insights into a potential basis for the negotiation process between the federal government and private corporations.

Chapter 2

Literature Review

Foundations of Cost-Effectiveness Analysis and Value-Based Pricing

Foundationally, cost-effectiveness analysis is built out of basic economics concepts of demand models. Wagstaff (1986) underlines the foundational "demand for health" approach describing health as a commodity the consumers have measurable demand for. He builds this theory around four concepts: the indifference map, the health production function, the budget constraint, and equilibrium. The indifference map is the starting point to explain that "good health is assumed to be desirable" but amidst a downward sloping indifference curve to represent that good health is not solely important over all else. As shown in Figure 1, there are natural tradeoffs between health and consumption as well as various indifference curves representing consumption preference.

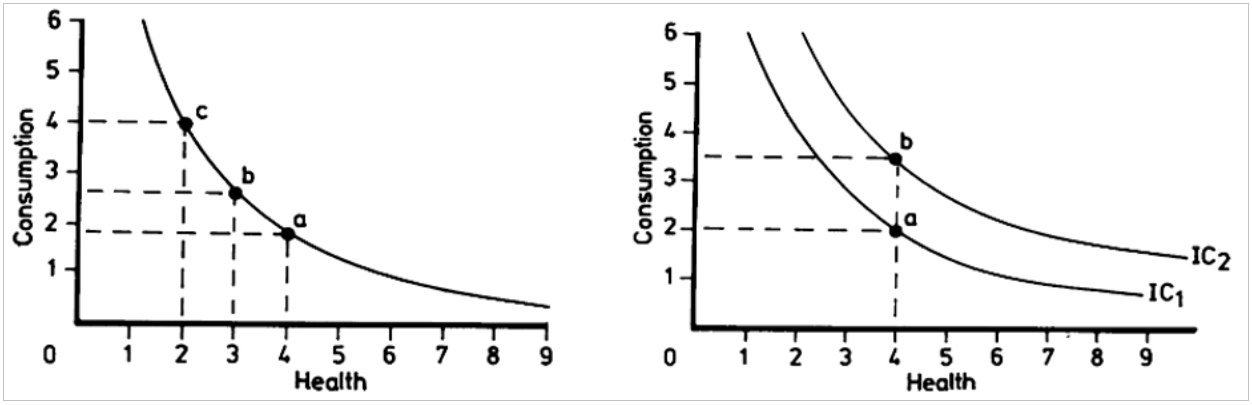

Figure 1 - Health Indifference Curves (Taken from Wagstaff (1986))

Wagstaff extends this approach into the health production functions where "individuals exert a relatively high degree of control over their health by virtue of the fact that they can influence their health-affecting consumption patterns, their health care utilization, and their environment." The individual's lifestyle and choices represent "health inputs" commonly mentioned as "bundles" so that increasing

health inputs increases units of health subject to diminishing marginal utility. However, the health production function depicts the result "for a given state of technical knowledge" which can change over time as health production becomes more efficient and the function shifts outwards in Figure 2.

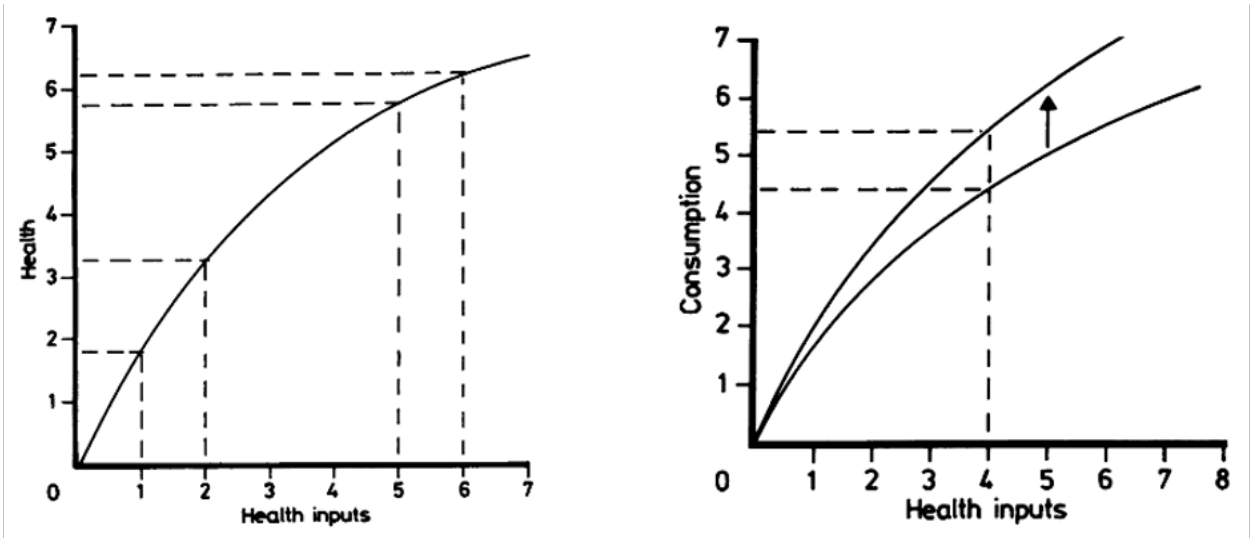

Figure 2- Health Production Functions (Taken from Wagstaff (1986))

The budget constraint introduces limited resources and key tradeoffs between health inputs and consumption defining the price of a health unit in terms of consumption. The budget constraint, Figure 3, helps define tradeoffs in addition to price changes in consumption or health inputs to reflect individual behavior and demand.

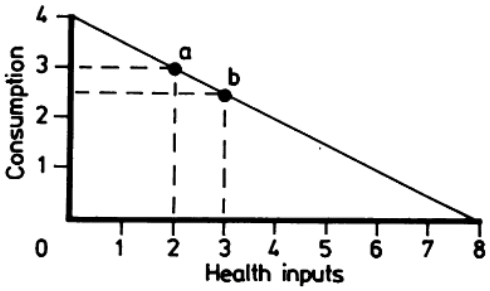

Figure 3 - Budget Constraint (Taken from Wagstaff (1986))

Combining the prior three concepts, the idea of equilibrium is introduced outlining four quadrants: indifference curves, the health production function, the budget constraint, and the consumption production function. As Figure 4 visualizes, the curve in quadrant one is the "welfare possibility frontier" indicating "all combinations of health and consumption which satisfy both the budget constraint and the health production function." Wagstaff continues that these combinations are "derived from the budget constraint

and the health production function" so they indicate all available to the individual who should be maximizing utility on the highest indifference curve available.

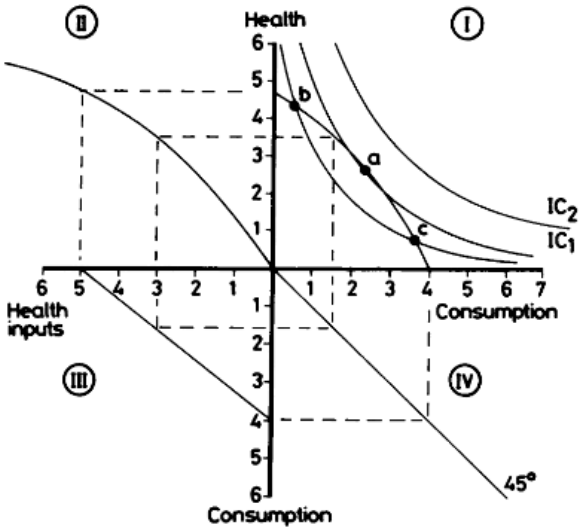

Figure 4 - Consumer Equilibrium Combination Diagram (Taken from Wagstaff (1986))

Moving from the "demand for health" into cost-effectiveness analysis highlights a crucial shift in the perspective of the individual to society as a whole. Weinstein (1977) describes that, at its core, cost-effectiveness analysis in health seeks "to maximize the total aggregate health benefits conferred… for any given level of resources available." Cost-effectiveness shifted away from strict dollar quantification of life, as done is cost-benefit analysis, to require that "health outcomes be expressed in commensurate units," such as the quality-adjusted life year (QALY), which became more "palatable to physicians." This new approach centers on the incremental cost-effectiveness ratio (ICER), which is the "ratio of the net increase in health-care costs to the net effectiveness in terms of enhanced life expectancy and quality of life." This approach takes into account discounting these future costs and health benefits through present-value analysis similar to financial asset pricing.

Incremental cost-effectiveness ratios (ICERs) became the focal point for cost-effectiveness analysis. As a reference point for overall economic budget impact, ICERs are always compared to thresholds based on health opportunity costs of losing QALYs due to the need to reallocate resources away from elsewhere in the health care system. Thresholds based on the marginal cost to produce a QALY differ around the world due to socioeconomic, demographic and healthcare system differences (Edney et al, 2022). For the United States, Vanness, Lomas, and Ahn (2021) estimated that for each additional $104,000 spent on a new therapeutic benefiting one group of patients, one QALY would be lost in the general population. Therefore, in the United States, new treatments benefiting patients but with an ICER greater than about $100,000 per QALY are unlikely to be cost-effective (Vanness, Lomas, Ahn,

2021). By modelling increases in healthcare expenditures, they simulated "morbidity attributable to individuals dropping health insurance due to increased healthcare expenditures passed through as premium increases." Pearson (2021) supports the importance of Vanness, Lomas, and Ahn (2021) by reiterating that "every added dollar the United States spends on health care may generate added health… [but] it also puts more pressure on health insurance premiums harming patients not in the room." Thus, all patients must be considered even if they are not immediately impacted.

Health Technology Assessment Agencies

Health technology assessment (HTA) agencies and related organizations, such as the Institute for Clinical and Economic Review (ICER) in the United States conduct cost-effectiveness analysis (CEA) to comment on the impact of new drugs on the nation's healthcare system. Ultimately, HTA seeks to maximize population health given a limited amount of resources available for healthcare, considering healthcare costs versus added health benefits. ICER's reviews seek to maximize health benefit while maintaining the level of healthcare costs due to the implications of higher insurance premiums leading to uninsured people. If a treatment can deliver superior health benefit for a feasible cost as juxtaposed with comparators, then it should be available within the healthcare system. However, if a treatment fails to deliver superior health benefit or cost efficicency, it could lead to higher insurance premiums and uninsure people leading to a net loss of population health welfare. Unlike other HTA agencies, ICER seeks to determine a price at which a treatment becomes a beneficial investment for society which is frequently much lower than the list price.

Outside of the United States, HTA agencies play a more influential role in healthcare policy and pricing. The National Institue of Health and Care Excellence (NICE) within the National Health Service in the UK conducts similar evidence-based research to provide recommendations to government agencies regarding coverage of health technologies and drugs at a particular price. NICE served as a model for

ICER; however, NICE appraisal is required for treatment funding by the National Health Service even though NICE does not hold explicit price-setting power. The Canadian Agency for Drugs and Technologies (CADTH) seeks to proide objective evidence to government decisionmakers but demonstrates a less significant tie to policy than NICE. Lastly, the Institute for Quality and Efficiency in Health Care (IQWiG) is the only government-linked HTA among the four discussed. While independent but under the government umbrella, IQWiG provides binding decisions on pricing using a framework similar to ICER's analysis in the United States. They try to show added therapeutic benefit in advance of price negotiations with a minimum discount from factory price. If benefit is shown, negotiations take place between the manufacturer and heath insurance funds. If benefit can not be shown, the drug is priced based on the average similar drugs.

Previous Systematic Literature Reviews

This thesis identified an existing systematic review of evidence published on costs, benefits, burden of disease, and treatments for psoriatic arthritis covering 2012-2017 using PubMed, EMBASE, and Cochrane Library and then updated it to include information published afterward. The review published by D'Angiolella et al. (2017) found 1652 references and included 9 cost-effectiveness analyses (CEAs) and 12 cost-of-illness studies. The review strategy used the following MeSH keywords across the three databases: "Psoriatic Arthritis" AND "cost" OR "cost effective" OR "cost utility" OR "burden" (D'Angiolella et al., 2017). Critical inclusion criteria highlight original economic evaluations of cost benefits, effectiveness, utility, and illness; psoriatic arthritis appraisal; and English language. Studies were excluded if data costs were limited to drug cost, the study contained other inflammatory diseases, and previously published systematic reviews. Across studies, patients with PsA "incur substantially higher direct and indirect costs compared to psoriasis without arthritis or other inflammatory diseases" with biologic interventions being a major predictor of cost." Additionally, biologic interventions were found to

be more effective than DMARDs for symptoms and quality of life improvement while also being more cost-effective because of cost offset due to efficacy and patient management improvements. However, additional biologic therapies available for treatment and in development may not follow these trends and may not be more cost-effective depending on the list price.

D'Angiolella et al. (2017) found nine CEAs on PsA which are most fundamental to this research on bimekizumab treating PsA. These studies fell largely into three categories: single/comparative treatment CEAs, CEAs for treatment-experienced patients, and CEAs of treatment timing. Four single/comparative treatment CEAs included secukinumab, golimumab, adalimumab, etanercept, infliximab, and ustekinumab. Three CEAs of treatment-experienced patients included TNF-α experience and DMARD failure. Two treatment timing studies included timely and delayed TNF inhibitor treatment and "tight control of inflammation" in early PsA (O'Dwyer, 2017).

Of the four single/comparative treatment studies, there was one comparative clinical efficacy study and three CEAs all from different perspectives and populations. Kirson et al. (2013) compared adalimumab, etanercept, and infliximab for PsA. Using differences-in-differences methodology between efficacy studies for each of the three treatments, adalimumab was associated with higher ACR70 and PASI50/75/90 than etanercept at week 24 and higher ACR70 than infliximab at week 14 (Kirson et al., 2013). In the U.S. and Germany, adalimumab treatment had lower cost per responder over multiple endpoints for both etanercept and infliximab (Kirson et al., 2013). Cummins et al. (2012) estimated the cost-effectiveness of golimumab from the UK NHS perspective using a decision analytic model. Compared to other TNF-α inhibitors, golimumab demonstrated comparable results; however, it was significantly superior to palliative care with a high probability of cost-effectiveness as an additional treatment option (Cummins et al., 2012). Goeree et al. (2017) analyzed the cost-effectiveness of secukinumab in the Canadian healthcare system using a decision analytic semi-Markov model that included treatment sequencing. Compared to a wide range of biologics, including adalimumab and golimumab, secukinumab was either dominant or cost-effective compared to all licensed biologics for

PsA (Goeree et al., 2017). Yang et al. (2016) compared etanercept, adalimumab, and golimumab using a meta-analysis of RCTs to calculate ICERs for each PsARC responder and each ACR20 responder. Looking at the Taiwan healthcare perspective, etanercept had the lowest annual cost per PsARC and ACR20 responder while adalimumab had the highest (Yang et al., 2016).

In addition to specific drug CEAs, additional studies in the D'Angiolella et al. (2017) reviewed separate patient populations such as TNF-α naïve patients, TNF-α experienced patients, or DMARD-failed patients. O'Connor et al. (2016) critiqued clinical and cost-effectiveness evidence on ustekinumab in TNF-α naïve and TNF-α experienced patient populations. This critique cited weakness in the original comparisons due to unreported network meta-analysis, uncertainty of model results, and lack of head-to-head comparisons. Ultimately, ustekinumab was only recommended if the manufacturer could provide it at the same cost for both 45mg and 90mg doses (O'Connor et al., 2016). Olivieri et al. (2016) and Corbett et al. (2017) both analyzed the costs and benefits of TNF inhibitors after patients had an inadequate response to conventional DMARD treatments. Olivieri et al. (2016) found that TNF inhibitors have long-term efficacy, and the higher cost of therapy was balanced in Europe by improvements in endpoints, but results need to be confirmed in a larger sample size. Corbett et al. (2017) focused on certolizumab pegol and secukinumab after DMARD failure in France using a systematic review and de novo model. Secukinumab and certolizumab pegol demonstrated clinically important efficacy in all key clinical outcomes and optimal treatment depended on disease severity and underlying assumptions (Corbett et al., 2017).

The final two CEAs from the D'Angiolella et al. (2017) review analyzed treatment timing over specific drug efficacy. O'Dwyer et al. (2017) analyzed the cost-effectiveness of "tight control of inflammation" in early PsA alongside a UK-based RCT to calculate mean costs and QALYs. Mean costs and QALYs were higher for the tight control group with tight control having only a 7% probability of being cost-effective at the UK threshold. Ultimately, it was found to be an effective strategy but not cost-effective. Strand et al. (2016) focused on TNF inhibitor use and evaluated costs and outcomes of timely

vs delayed use in moderate to severe PsA from the U.S. payer perspective. Patients were started on one of four TNFi drugs ("timely" TNFi use), or started on apremilast before moving to a TNFi in non-responders ("delayed" TNFi use). Timely TNFi use was associated with higher endpoints and higher costs in PsA patients resulting in cost-effectiveness based on improvements (Strand et al., 2016).

This thesis updated the D'Angiolella et al. (2017) systematic review to identify newly published psoriatic arthritis cost-effectiveness analysis. This new review searched for original studies and analyses in PubMed, Cochrane Library, Web of Science, and the Tufts Medical Center Cost Effectiveness Analysis (CEA) Registry published from October 2017 to January 2024. EMBASE could not be included due to cost-prohibitive access; however, there should not be significant gaps in search results due to the volume available across the other databases. Subject headings (MeSH terms) were used where possible to maximize search results: "Psoriatic arthritis" AND "cost" OR "cost effective" OR "cost utility" OR "burden" OR "economic" OR "pharmacoeconomics" OR "cost-benefit analysis" OR "cost-effectiveness analysis" OR "economics, pharmaceutical" OR "cost of illness" NOT "pharmacodynamic" OR "pharmacokinetic." The search strategy manually added time constraints from October 2017 to January 2024 to the search code:

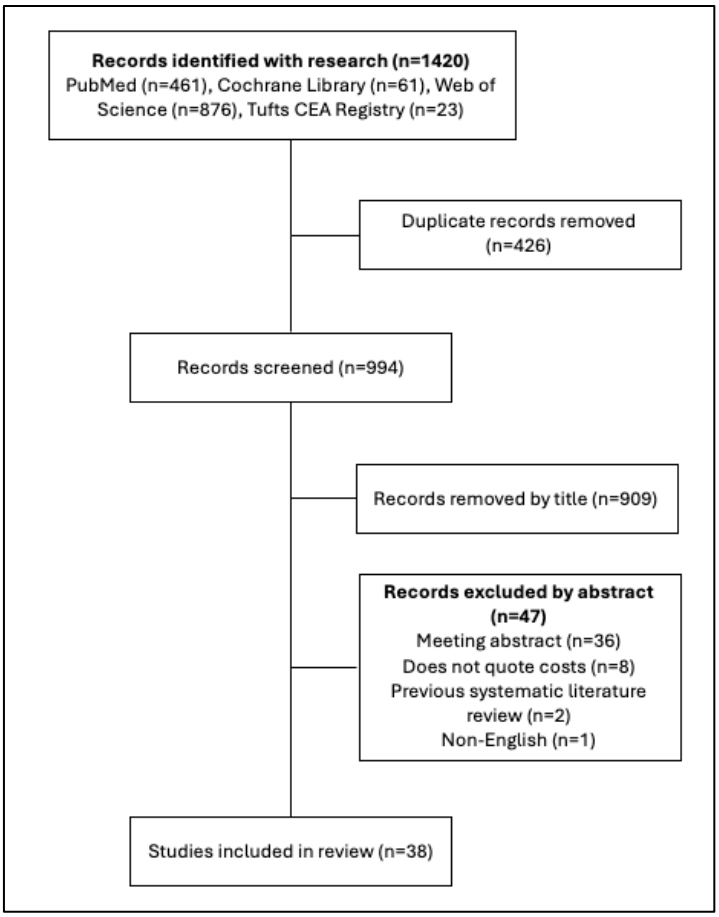

Figure 5 - Systematic Review PRISMA Diagram for Selection

(("Arthritis, Psoriatic"[Mesh]) OR (psoriatic arthritis[Title/Abstract])) AND ((((((("Economics"[Mesh] OR "Cost-Benefit Analysis"[Mesh]) OR "Cost-Effectiveness Analysis"[Mesh]) OR "Cost of Illness"[Mesh]) OR "Economics, Pharmaceutical"[Mesh]) OR (cost[Title/Abstract] OR cost effective[Title/Abstract] OR cost utility[Title/Abstract] OR burden[Title/Abstract] OR economic[Title/Abstract] OR pharmacoeconomics[Title/Abstract] OR cost benefit analysis[Title/Abstract] OR cost effectiveness analysis[Title/Abstract] OR pharmaceutical economics[Title/Abstract] OR cost of illness[Title/Abstract])) NOT (pharmacodynamic OR pharmacokinetic))

The search terms returned n=1420 results as broken down by database:

- PubMed n=461
- Cochrane Library n=61
- Web of Science n=876
- Tufts CEA Registry n=23

The systematic approach involved multiple stages of article review as demonstrated by the PRISMA diagram in Figure 5. After collecting all results, n=426 duplicate articles were removed. After removing duplicates, title screening removed unrelated topics to screen out n=909 papers. The title review removed articles that focused on other diseases, comorbidities, non-pharmaceutical interventions, and non-focus symptoms. Following the title review, abstract review excluded n=47 articles by criteria including meeting abstracts, not quoting costs, previous systematic literature reviews, and publication not being in English. Before conducting a full-text review phase of the remaining 38 articles, a systematic review and network meta-analysis of the comparative efficacy and safety of bimekizumab for psoriatic arthritis published by Mease et al. (2024) was examined in detail.

Mease et al. (2024) conducted a systematic literature review up to January 2023 identifying RCTs of b/tsDMARDs and used Bayesian network meta-analysis for efficacy outcomes in b/tsDMARD-naïve and TNFi-exp patients. Collecting similar results to this thesis's update, the Mease et al. (2024) review

included 41 RCTs for 22 b/tsDMARDs ranking outcomes for minimal disease activity (MDA), ACR20/50/70, PASI90/100, and serious adverse events. The review concluded that "bimekizumab ranked favorably among b/tsDMARDs for efficacy on joint, skin, and MDA outcomes and showed comparable safety" which indicates potential for great cost effectiveness in the structural model this thesis develops. The review serves as a baseline for efficacy data of bimekizumab and comparators on the TNFi-exp patient population included in Sigurdardottir et al. (2023) which translates into this thesis's structural and simulation model.

Sigurdardottir et al. (2023), a cost-effectiveness study on bimekizumab in the context of the Swedish healthcare system, focuses on two patient populations: bDMARD-naïve patients and TNFi-exp patients. Using a standard Markov model, the study analyzed primary response outcomes ACR50, PASI90/75, and PASI50/<50 where failure to meet ACR50 or PASI90/75 warranted treatment switching. The model exhibited results that BKZ is widely cost-effective and/or dominant against other treatments. In bDMARD-naïve patients, BKZ achieved greater QALYs than all competitors, either dominating or being cost-effective against, except being dominated by infliximab in the base case scenario. In TNFi-exp patients, BKZ achieved greater QALYs than all competitors. BKZ either dominated or was cost-effective against all comparators except certolizumab pegol. This model structure serves as a framework for this thesis's research in the United States setting.

Chapter 3

Structural Model

Markov Decision-Analytic Model

The model discussed in this section is based on a similar model of cost-effectiveness analysis of bimekizumab for the treatment indication of psoriatic arthritis developed by Sigurdardottir et al. (2023). Using this model as a template considering interventions and comparators as well as treatment sequence and clinical characteristics, this thesis adapts the model to fit the United States environment with different population and economic considerations. As a state-transition cohort model, the model simulates the clinical and treatment sequence of a patient diagnosed with PsA. Sigurdardottir et al. (2023) adapted a York model framework for the treatment of PsA from Rodgers et al (2011). The York principles outline dimensions of quality, attributes of good practice, and questions for critical appraisal across elements of structure, data, and consistency in a model (York Center for Health Economics, 2016). These principles are used in the construction of the framework for decision-analytic models, such as Markov models, and incorporates elements of uncertainty, probability, costs, and health measures.

Markov models are commonly used in the cost-effectiveness evaluation of healthcare technologies such as pharmaceutical interventions. Markov models depict disease progression in a patient (or an identical cohort of patients) on a given treatment and aim to incorporate all possible outcomes of moving through a disease. This progression is set up using mutually exclusive and exhaustive disease states, which are different classes that a given patient can fall in based on symptom measurement. For example, “health states that might be included in a simple Markov model for a cancer intervention are: progression-free, post-progression, and dead” (York Center for Health Economics, 2016*).* Time in a Markov model is broken down into “cycles” which is the certain number of weeks or months between transition probabilities. At each cycle, there are transition probabilities which represent the likelihood for any given patient to move from their current disease state into another disease state which has associated

costs and health outcomes. This model is expanded to consider a cohort of patients so that the model aggregates patient experiences which can then be compared to another treatment.

This thesis uses an adaptation of the Markov model aligning with Sigurdardottir et al. (2023), to simulate the clinical pathway of a tumor necrosis factor inhibitor experienced (TNFi-exp) PsA patient over a lifetime horizon of 50 years. While Sigurdardottir et al. (2023) model two subgroups of patients: (1) b/tsDMARD-naïve and (2) TNFi-exp, this thesis simplifies this analysis to solely TNFi-exp patients for a narrower scope. Using a state-transition cohort model, the model recreates "the chronic nature of PsA and [incorporates] the effects of therapies on both skin and joint symptoms." The hypothetical cohort of patients is characterized using phase 3 clinical data, "BE COMPLETE," from Merola et al. (2023) and modeled over a lifetime horizon of 50 years. This lifetime horizon is broken down into two periods: 1) a shorter-term induction period from treatment initiation to the first symptom evaluation of both joint and skin measures and 2) a longer-term maintenance period where patients continue treatment until a patient discontinues due to inadequate treatment efficacy or adverse events. Discontinuation is aggregated as a single probability per year.

This U.S.-based Markov model maintains similar assumptions to Sigurdardottir et al. (2023). Patients stay on treatment through the induction period and do not discontinue until after the induction period at the earliest. If a patient does not respond, they switch back to concomitant csDMARDs. The Sigurdardottir et al. (2023) model splits the induction period into different cycles:

1. Induction to end of maximum response on physical function in the initial response period (four weeks)
2. To the end of the initial response period (13 weeks)
3. End of initial response period to end of week 39
4. End of week 39 to week 52

After the four-cycle breakdown of the first full year, the model uses a one-year cycle length. Patients can die at any time associated with a probability of death by "adjusting general population

mortality estimates in Sweden with a PsA-specific mortality rate ratio of 1.05" (Sigurdardottir et al., 2023). In this model, I am adjusting 2021 United States Life Table population mortality estimates from Arias et al. (2023) with the same PsA-specific mortality rate ratio of 1.05 as concluded by Ali et al. (2007). The model then runs each cycle through until age 100.

As displayed in Figure 6, the model begins by prescribing a treatment indication, bimekizumab or specified comparator, for which the model will run for any given treatment sequence. Following the same health state breakdown for any treatment indication selected, the first criteria is ACR50 response to measure joint symptom elements of the treatment. Whether meeting or failing to meet, the sequence then moves to assess PASI response to measure skin symptom elements. If failing to meet ACR50, the PASI level is measured at one of four thresholds: PASI<50, PASI50, PASI75, or PASI90. If failing to meet ACR50, the sequence ends at the end of the initial response period in switching treatment back to csDMARDs regardless of the level of PASI response.

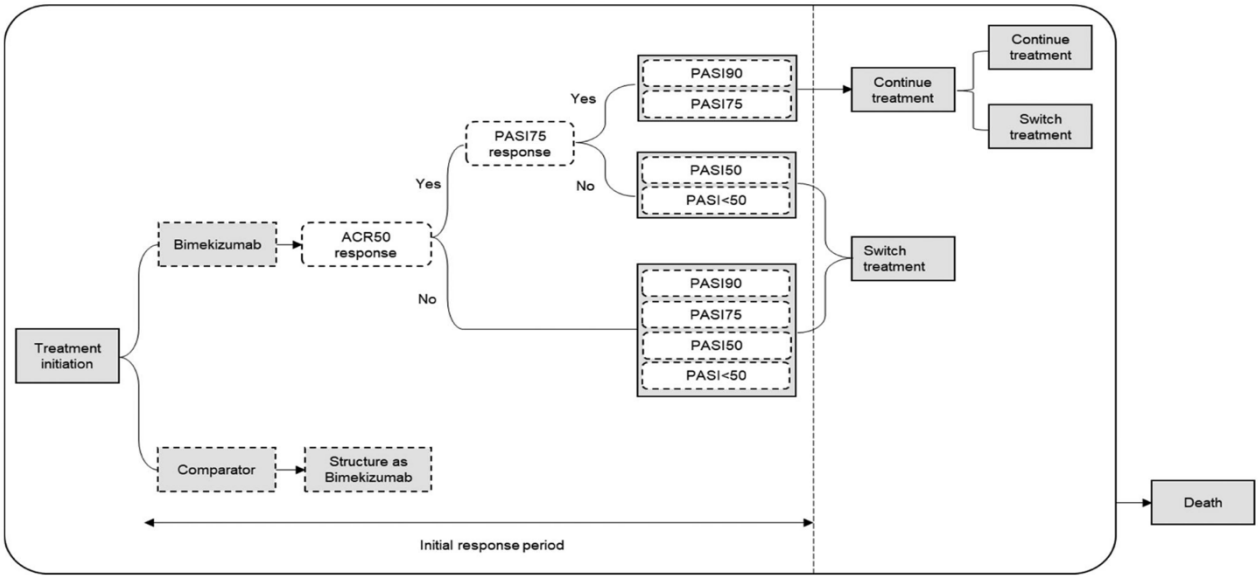

Figure 6 - Markov model structure (Taken from Sigurdardottir et al. (2023))

If the sequence meets ACR50 response, it will first move to assess specifically the PASI75 level of skin symptom. The PASI75 assessment then breaks the sequence into two paths: PASI<50 and PASI50 responders switch treatment at the end of the initial response period whereas PASI75 and PASI90

responders continue treatment following the end of the initial response period. The sequence continues on the prescribed treatment and follows a constant treatment discontinuation probability, “26% per annum assumed equal for all treatments”, that Sigurdardottir et al. (2023) derives from a drug-survival study published by Egeberg et al. (2022).

Chapter 4

Data

Phase III Clinical Data: Bimekizumab for Psoriatic Arthritis

The two phase 3 clinical trials published by McInnes et al. (2023) and Merola et al. (2023) evaluate bimekizumab's efficacy as an intervention for PsA. Both studies are RCTs that study the efficacy and safety of BKZ in patients compared to placebo. Each study was constructed as a 52-week multicenter, randomized, double-blind, placebo-controlled trial across different sites and countries. Trial-eligible patients were 18+ years old with a documented diagnosis of adult-onset psoriatic arthritis that met the Classification Criteria for Psoriatic Arthritis (CASPAR) at least 6 months before screening. CASPAR was established from a 2006 international study to construct new criteria from observed data (Taylor et al., 2006). The CASPAR criteria consist of "established inflammatory articular disease with at least three points from the following features:

> Current psoriasis (assigned a score of 2; all other features were assigned a score of 1), a history of psoriasis (unless current psoriasis was present), a family history of psoriasis (unless current psoriasis was present or there was a history of psoriasis), dactylitis, juxta-articular new bone formation, rheumatoid factor negativity, and nail dystrophy (Taylor et al., 2006)

A retrospective study of the CASPAR criteria demonstrates that the "feasibility, specificity, and sensitivity of the CASPAR are maintained when adapted for retrospective use to classify an established research cohort" (Tillet et al., 2012).

The McInnes et al. (2023) study, titled "BE OPTIMAL" assessed the efficacy and safety of BKZ in "patients who were naïve to biologic disease-modifying antirheumatic drugs (bDMARDs)" (McInnes et al., 2023). This study used active reference (adalimumab), and patients were randomly assigned to bimekizumab every 4 weeks, placebo every 2 weeks, or reference (adalimumab) every 2 weeks. Its primary endpoint was the proportion of patients reaching 50%+ improvement in ACR50 criteria at week

16. BKZ treatment showed "superior improvements in joint, skin, and radiographic efficacy outcomes at week 16" compared to placebo; however, BKZ did not show superior improvements to those receiving reference (adalimumab). The safety profile was consistent with previous phase 3 studies for plaque psoriasis with IL-17A inhibitors.

The Merola et al. (2023) study "BE COMPLETE" focuses on this study's population of interest: patients with active PsA and previous inadequate response or intolerance to TNF-α inhibitors. Eligibility criteria required a history of inadequate response/intolerance to treatment with one or two TNF-α inhibitors. Patients were randomly assigned to BKZ or placebo with the same primary endpoint as McInnes et al. (2023) of "proportion of patients reaching ACR50 criteria at week 16" The study finds that "BKZ treatment led to superior improvements in joint and skin efficacy outcomes at week 16 compared with placebo" in the specified patient population with a consistent safety profile to McInnes et al. (2023).

BE OPTIMAL and BE COMPLETE identify similar results for BKZ treatment on PsA in different patient populations. BE OPTIMAL identifies superiority over placebo, but not over reference treatment in the bDMARD-naïve population and BE COMPLETE similarly identifies superiority over placebo in a TNF-α-naïve population. BE COMPLETE also identifies efficacy in a narrowed population of patients as "conventional DMARDs suppress the overall immune system, whereas biologics [such as TNF-α inhibitors and IL inhibitors,] block specific parts of the immune system, such as proteins that promote inflammation" (Rath). Each of these studies introduces new efficacy data about BKZ over placebo and over a reference treatment which could impact the value-based price for BKZ and in turn its cost-effectiveness compared to the next best available treatment for PsA. These clinical results input new efficacy into a calculation of clinical outcomes and the cost-effectiveness of those outcomes against healthcare system perspectives.

Economic value is derived from all available information immediately factored into the calculation of the value of an asset such as a clinical treatment. As such, cost-effectiveness analyses need to include the most up-to-date data on efficacy, costs, and comparators to be most impactful. BE

OPTIMAL and BE COMPLETE results have been used in a cost-effectiveness analysis from the Swedish healthcare system perspective. This Swedish study compares BKZ to a range of immune-suppressing biologic and targeted synthetic biologic DMARDs (ts/bDMARDs) in bDMARD-naïve and TNFi-exp patient groups (Sigurdardottir et al., 2023):

- Previously reimbursed TNFis: adalimumab original and biosimilar, certolizumab pegol, etanercept original and biosimilar, infliximab original and biosimilar, and golimumab
- Interleukin 17A inhibitors (IL-17Ais): ixekizumab, secukinumab 150mg and 300mg
- Interleukin 23 inhibitors (IL-23is): guselkumab 100mg Q8W and Q4W, risankizumab
- Interleukin 12/23 inhibitors (IL-12/23is): ustekinumab 45mg and 90mg
- Janus Kinase inhibitors (JAKis): upadacitinib and tofacitinib
- Abatacept
- csDMARDs

Competitor Network Meta-Analysis

The efficacy data in this thesis is derived from BE OPTIMAL for bDMARD-naïve patients and BE COMPLETE for TNFi-exp patients while using network meta-analysis to derive competitor efficacies (Sigurdardottir et al., 2023). Mease et al. (2024) conducted a systematic literature review of RCTs of b/tsDMARDs in PsA using Bayesian network meta-analyses for efficacy outcomes in both b/tsDMARD-naïve and TNFi-experienced patient populations. The systematic review "utilized odds ratios and differences of mean change with the associated 95% credible interval… for the best-fitting models, and the surface under the cumulative curve (SUCRA) values were calculated to determine relative rank (Mease et al., 2024). The network meta-analysis included 41 RCTs for 22 b/tsDMARDs and analyzed minimal disease activity (MDA), ACR20/50/70, PASI90/100, and serious adverse events. Figures 4 and 5,

respectively, depict ACR50 and PASI100 results from the Mease et al. (2024) NMA at week 16 that inform efficacy data incorporated into the Sigurdardottir et al. (2023) cost-effectiveness analysis of BKZ.

For consistency with model inputs, this thesis hold many of the assumptions from Sigurdardottir et al. (2023) regarding HAQ-DI and PASI trajectories constant:

- "Patients achieving both an ACR50 and PASI75 response at the end of the induction period were assumed to stay on treatment and to experience a reduction in their baseline HAQ-DI and PASI scores at that point"
- "The induction HAQ-DI change was assumed to be achieved by week 4 of treatment"
- "For TNFi-exp patients, HAQ-DI was assumed to remain stable after induction while on treatment due to the absence of treatment-specific data after week 16 in BE COMPLETE"

Cost Inputs

Using the ICER organization 2023 Value Assessment Framework and the associated 2023 Reference Case for Economic Evaluations, this thesis follows guidelines on the incorporation of resource use and costs based on the health system perspective for costs paid by third-party payers. The Reference Case identifies specific language for "branded treatments that do not require provider administration and a price is known" that the "treatment acquisition list price should be equivalent to the average WAC across all formulations" (ICER, 2023). The guidelines also dictate an order of methods to calculate a net price. ICER recommends beginning with average discount data obtained from SSR Health, LLC, but as that is unavailable for the context of this research, this thesis uses the Federal Supply Schedule (FSS) to calculate the discount between the WAC price and FSS price. The Federal Supply Schedule is publicly available through the U.S. Department of Veterans Affairs' Office of Procurement, Acquisition, and Logistics (OPAL). As the best available substitute, the FSS represents the U.S. public healthcare system

perspective on drug costs incurred by insurance coverage. It serves as a standard average discount for this public perspective in the model calculations.

2023 weighted average cost (WAC) prices, or "list prices," were publicly available on the drug/manufacturer websites for bimekizumab and all comparator interventions. WAC and FSS prices were collected for all TNFi-exp patient comparator drugs cited in Sigurdardottir et al. (2023). According to the ICER Value Assessment Framework Guidelines, the process computed the average FSS contract price of each drug in its specified dosage strength formulation. Using this average price for each dose in the TNFi-exp patient comparator list, the process multiplied them out over the posology defined by Sigurdardottir et al. (2023) to find annual cost in Year 1 and Year 2+. The average new prices as computed from the FSS are used in the conventional base-case and sensitivity analyses for cost-effectiveness analysis according to ICER (2023). Moreover, the WAC costs are used in the calculation of discounts needed to reach health-benefit price benchmarks (HBPB) such as a value-based price derived from an ICER threshold. If a WAC is above the HBPB, the drug does not provide the expected clinical benefit for the price based on the analysis and would not improve population welfare. This is further discussed in the Value Based Pricing Analysis section of Chapter 6.

Chapter 5

Simulation Model

The simulation model for this thesis uses a Markov model aligning with Sigurdardottir et al. (2023), to simulate the clinical pathway of a TNFi-exp PsA patient over a lifetime horizon of 50 years. Built in Microsoft Excel, the model breaks down the simulated cohort of patients into 61 groups based on their clinical response criteria of ACR50 response and PASI50/75/90 response. ACR response is classified as response greater than or less than 50. PASI response is classified as 90, 75, 50, or less than 50. Groups are broken down into the following:

- Achieving ACR50 and some level of PASI while on treatment [4]
- Not achieving ACR50 and some level of PASI while on treatment [4]
- Not achieving ACR50 and off treatment [1]
- Discontinuing treatment immediately after induction [1]
- Off treatment for each time period in the lifetime horizon [50]
- Dead [1]

The off treatment groups move sequentially where if a patient discontinues treatment, they will always begin at off treatment n=1 and each year progress to the next state n+1 while others may discontinue and then begin at n=1. At all times in the model, the sum of all groups equals the beginning population. This thesis selected comparator drugs based on comparable clinical data to bimekizumab: csDMARDs assumed to be methotrexate, ustekinumab 90mg (UST_90), ixekizumab (IXE), upadacitinib (UPA), certolizumab pegol (CZP). An independent Markov model is constructed for each drug and follows state transitions in Figure 7.

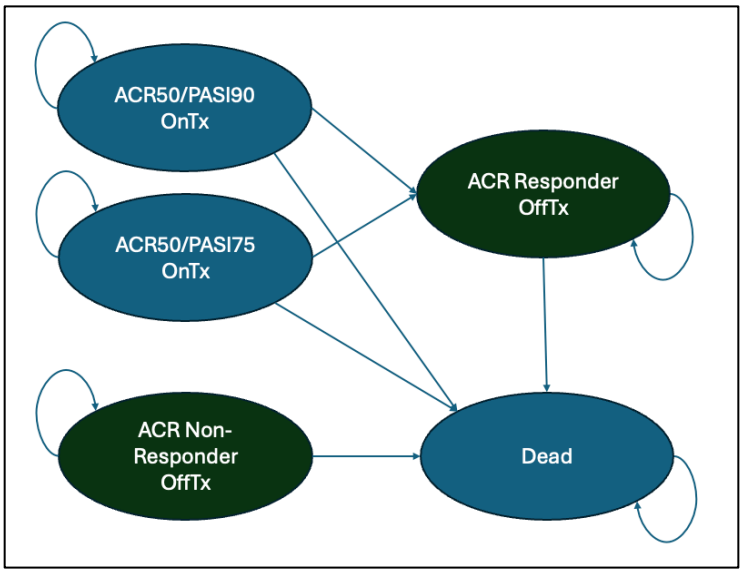

Figure 7 - State Transition Diagram

(Green states for OffTx track time spent in the state to compute HAQ-DI trajectory). Tx: Treatment

State Populations

The model begins with the simulated patient population starting age as 50 years old based on results reported in Sigurdardottir et al. (2023). This is modeled as t=0 and extends over a 50-year lifetime horizon to age 100. The first year is broken down by the induction process spelled out in Sigurdardottir et al. (2023). This separates the first year into the following periods: Weeks 0-4, Weeks 4-13, Weeks 13-39, Weeks 39-52. The induction period ends at week 39 and after the first year the model continues in full-year cycles.

The first stage in both models breaks down group population over the 50-year horizon to determine the percentage of patients with each clinical response, or dead, at each age. Group population is determined by prior period population, a relative risk of death for PsA patients, an age-based risk of death in the U.S., and the probability of discontinuing treatment for groups that are “on treatment.” The model assumes that patients do not discontinue treatment until after the induction period of 39 weeks. The model also assumes that patients do not die until after the induction period.

QALY Calculation

The second stage of both models computes the HAQ-DI score for each population group in each period of the lifetime horizon. The model assumes the mean population score at t=0. Patients that achieve ACR50 response experience a score reduction that remains constant as long as they remain on treatment. The model also assumes patients do not return to their baseline score and instead begin a downward trajectory of HAQ-DI immediately after discontinuing treatment. Patients that experience ACR less than 50 response face a smaller reduction in score than those that do meet ACR50 and follow the standard progression as laid out.

The third stage of the model computes PASI score for each population group in the same structure as the population measures and HAQ-DI scores. Each group begins with the mean population score at t=0 and experiences reductions based on their level of PASI50/75/90 response. When patients discontinue treatment, they return to their baseline score. There is no progression of scores beyond the initial response to treatment or change in response due to discontinuation.

The fourth stage of the model uses the prior three stages to compute the EQ-5D score for each population which directly factors into the computation of QALYs for each group. EQ-5D uses an exponential equation and the parameters described in Sigurdardottir (2023). As such,

$$logit(EQ-5D) = 2.361 - .821 * HAQDI - .03 * PASI + .017 * HAQDI * PASI - .095 * SEX$$

where SEX=1 for female and SEX=2 for male. The model for this thesis uses a logistic regression:

$$EQ-5D = e^{logit(EQ-5D)}/(1 + e^{logit(EQ-5D)})$$

Anyone in the dead stage is assigned EQ-5D = 0. Using the group populations, undiscounted EQ-5D is calculated for each time period by summing the multiplications of each group population by their corresponding EQ-5D score. QALYs are then calculated as EQ-5D for the state multiplied by time spent in the state (4 different time periods related to the induction phase during the first year of the model, and one year time cycles in the long-run phase of the model) change in time. QALYs are then discounted using a U.S. standard discount rate of 3% per year for QALYs as well as costs.

Costs and Resource Use

The fifth stage of the model calculates costs for each group and time period. It is assumed at t=0 that patients do not incur any cost and patients who are on treatment begin the TNFi drug alongside methotrexate which is used to represent a concomitant DMARD. Costs are calculated using the sum of drug costs, the sum of treatment monitoring services, and a cost associated with the level of HAQ-DI the patient is experiencing. Drug costs are calculated using averages from the Federal Supply Schedule (FSS) with posology derived from Sigurdardottir et al. (2023). Costs are assigned using the difference in time periods to determine the number of treatments necessary in that period. Treatment monitoring services include full blood count, liver function test, urea and electrolytes test, chest radiograph, and tuberculosis blood test. Costs are derived from the average of Medicare Part B claims data with posology from Sigurdardottir et al. (2023). Supportive care treatment costs are assumed to vary by HAQ-DI (worse HAQ-DI generally meaning more severe disease and higher care costs) and are modeled using data from Ogdie et al. (2022) which provides the mean medical costs as a sum of hospitalization, emergency department visits, outpatient visits, diagnostic tests, and procedures. Ogdie et al. (2022) models costs based on a mean score similar the BKZ clinical population and this thesis uses the costs associated with a one-point in HAQ-DI score to derive a function of these costs per HAQ-DI level as visualized in Figure 8.

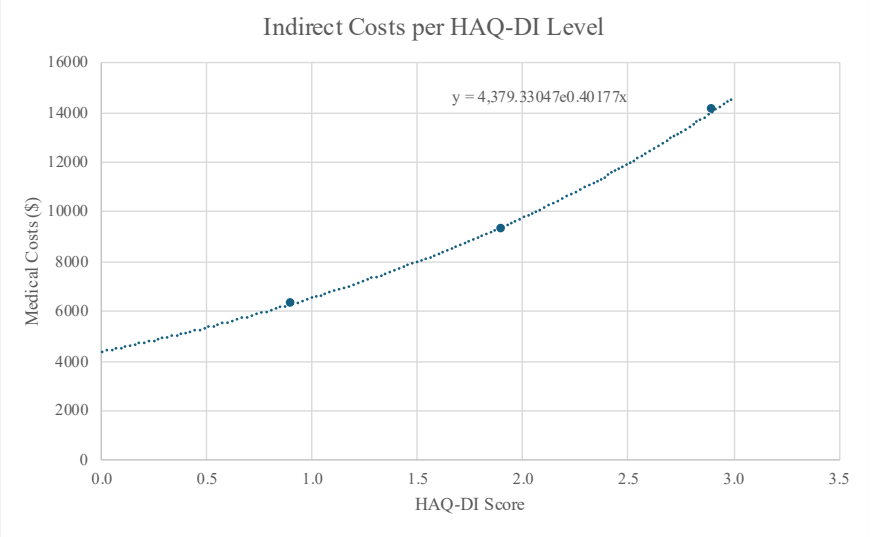

Figure 8 - Indirect Medical Costs per HAQ-DI Score derived from Ogdie et al. (2022)

ICER Ratio Comparison

For each drug's Markov model, discounted QALYs and discounted costs by time period are each summed for all years to obtain total discounted costs and QALYs. Following this summation, drugs are ordered according to total discounted QALYs are plotted against total costs. If any drugs provide higher QALYs at a lower cost than the one prior, it is considered to be "dominated" and an ICER ratio is not reported. ICER ratios are computed for non-dominated drugs by comparing the next higher QALYs to baseline and dividing incremental costs by incremental QALYs. Then, the comparison shifts to the next non-dominated drug and compares to the higher QALYs. However, the comparator drug cannot be dominated, thus, the comparator drug changes between each ICER calculator as dominance is exhibited. A drug is considered extended dominated if it is dominated by a linear combination of a drug with lower QALYs and a drug with higher QALYs. That is to say, the extended dominated drug has a higher ICER ratio than another compared to the same reference point.

Any drugs that are not dominated or extended dominated at the end of the ICER analysis are considered to remain on the cost-effectiveness frontier. Each of the drugs on the frontier provide different levels of effectiveness (in QALYs) at different total costs. Drugs that were removed from the cost-effectiveness frontier in the ICER calculation process do not exhibit adequate effectiveness gains in relation to total costs. This could be because of another drug dominating it with higher effectiveness and lower cost. This could also be due to extended-dominance where another drug exhibits a lower ICER when compared to the same baseline.

Chapter 6

Simulation Results

To create a cost-effectiveness evaluation and comparison, the thesis created models for bimekizumab (BKZ) and comparator models for csDMARDs (assumed to be methotrexate), upadacitinib (UPA), certolizumab pegol (CZP), ixekizumab (IXE) and ustekinumab 90mg (UST_90). The Markov model structure is held constant across the six drugs with changes in the parameters for probability to achieve ACR50 and PASI50/75/90 found in Appendix D. The drug cost and dosage vary by intervention with the concomitant DMARD, methotrexate, held constant. Medical services frequency and costs remain constant and the indirect cost associated with HAQ-DI continues to vary according the model established in Chapter 5.

Each model sums the total discounted costs and total discounted QALYs across all time periods t=0 to t=50 for all ages 50-100. Incremental costs and QALYs are calculated as the difference between bimekizumab and the comparator. Following this, the incremental cost effectiveness ratio (ICER) is computed as incremental costs divided by incremental QALYs. As cited in the ICER organization's Value Assessment Framework, calculated ICER ratios are compared to a range of thresholds from $50,000 to $200,000 per QALY as a measure of value. If a calculated ratio exceeds a selected threshold, the drug would be evaluated as non-cost-effective because of the cost burden placed on societal health insurance as compared to the value gained by treating a particular disease or health burden.

Figure 9 displays the model results across the six comparator drugs. Plotted with QALYs on the x-axis, the slope between any two treatments is equal to the ICER ratio of incremental costs divided by incremental effectiveness.

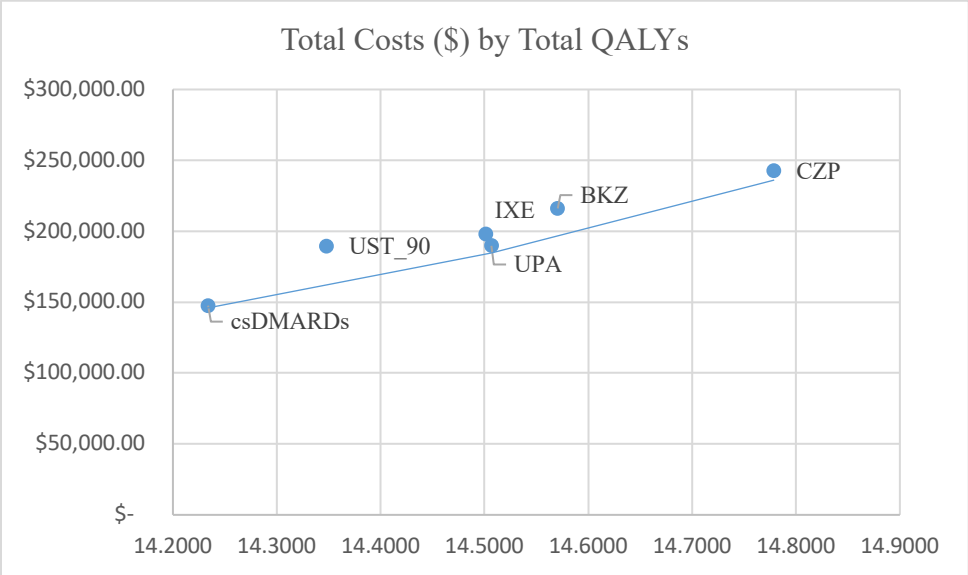

Figure 9 - Model Results for Total Costs and Total QALYs

Table 1 depicts the ICER ratio analysis based on the plotted results from Figure 9. Ordered in terms of total QALYs, csDMARDs begins as the comparator drug. The ICER for UST_90 is calculated as incremental costs divided by incremental QALYs compared to csDMARDs. The ICER for IXE vs UST_90 becomes unreportable because when IXE is compared to UPA, UPA exhibits higher total QALYs at a lower total cost and therefore dominates IXE. The ICER for UPA is compared to csDMARDs and exhibits extended dominance* of UST_90. The linear combination of csDMARDs and UPA is of greater cost-effectiveness (lower ICER ratio) than UST_90 compared to csDMARDs. Similarly, BKZ is extended dominated by the linear combination of UPA and CZP, exhibiting greater cost-effectiveness that the ICER for UPA and BKZ. Lastly, CZP is compared to UPA because it must be compared to a non-dominated intervention. Interestingly, but not uncommon, none of the remaining drugs on the cost effectiveness frontier meet the base case $100,000/QALY threshold.

Table 1 - ICER Ratio Analysis

Intervention	Total QALYs	Total Costs ($)	ICER ($/QALY)	Comparator
csDMARDs	14.2339	$ 147,559.14	-	-
UST_90	14.3479	$ 189,391.21	extended dominated	UPA and csDMARDs
IXE	14.5011	$ 198,081.06	dominated	UPA
UPA	14.5067	$ 189,742.28	$ 154,639.84	csDMARDs
BKZ	14.5705	$ 216,097.16	extended dominated	UPA and CZP
CZP	14.7787	$ 242,659.90	$ 194,536.66	UPA

Value Based Pricing Analysis

To further evaluate the cost-effectiveness of BKZ, the results include a sensitivity analysis of the input prices for BKZ and the impact on its ICER ratio. The goal of this analysis is to find the value-based price which is the price for a drug to meet certain ICER thresholds with its measured effectiveness. To best replicate the Medicare negotiation process laid out in the Inflation Reduction Act, the analysis compared bimekizumab to the minimally effective standard of care which is csDMARDs assumed to be methotrexate. This comparison comes from the fact that csDMARDs are much less effective than biologic drugs and are frequently used in conjunction with one another. The analyses uses ICER thresholds of $100,000/QALY, $150,000/QALY, and $200,000/QALY to best represent the U.S. payer perspective and earlier research by Vanness, Lomas, Ahn (2021) that the U.S. ICER threshold likely falls within $100,000-$150,000/QALY. The $100,000/QALY threshold is idealistic for a drug based on this research, and upper thresholds of $150,000/QALY and $200,000/QALY represent extension of coverage more realistic to the U.S. healthcare system payer perspective. The variety of ranges inform different value based prices and targets.

Table 2 displays the ICER for csDMARDs and BKZ and the analysis uses Microsoft Excel “Goal Seek” to adjust the price per pack of BKZ and set the ICER equal to $100,000/QALY. This analysis results in a value-based price-per-pack (2 doses) of $5,872.87 for BKZ and a unit price of $2,936.44. This

input underlines new total costs of $181,222.85 alongside unchanged QALYs to set the new ICER. Likewise, Table 3 finds a price-per-pack of $8,240.79 and a unit price of $4120.40 for the $150,000/QALY ICER. Table 4 finds a price-per-pack of $10,608.71 and a unit price of $5304.36 for the $200,000/QALY ICER.

Table 2 - $100,000 ICER Base Case Analysis of BKZ Cost

Intervention	Total QALYs	Total Costs ($)	ICER ($/QALY)
csDMARDs	14.2339	$ 147,559.14	-
BKZ	14.5705	$ 181,222.85	$ 100,000.00

Table 3 - $150,000 ICER Sensitivity Analysis of BKZ Cost

Intervention	Total QALYs	Total Costs ($)	ICER ($/QALY)
csDMARDs	14.2339	$ 147,559.14	-
BKZ	14.5705	$ 198,054.70	$ 150,000.00

Table 4 - $200,000 ICER Sensitivity Analysis of BKZ Cost

Intervention	Total QALYs	Total Costs ($)	ICER ($/QALY)
csDMARDs	14.2339	$ 147,559.14	-
BKZ	14.5705	$ 214,886.55	$ 200,000.00

The sensitivity analysis assists in the computation of a range of value-based prices at different incremental cost-effectiveness ratios over the standard of care baseline. The range of price-per-pack and unit prices ultimately help provide guidance to a manufacturer or insurance company about the price they should be willing to charge or pay for the drug.

Discussion of Results

The results of the BKZ analysis are an insightful comparison to that of the Sigurdardottir et al. (2023) study published from Sweden. Compared to this other study, BKZ is not able to exhibit

dominating cost-effectiveness against all chosen competitors. While delivering the second-highest QALY effectiveness, it falls short of reaching CZP as it also does in Sigurdardottir et al. (2023). When BKZ and CZP are individually compared to UPA, it uncovers that CZP extended dominates BKZ due to the ICER ratios of each comparison to UPA. That is to say that CZP is a more effective increment for QALYs and costs than BKZ is. Following the analysis, the only remaining treatments on the cost-effectiveness frontier are csDMARDs, UPA, and CZP as visualized by the connecting line on Figure 8. These three treatments exhibited cost-effectiveness against other available through dominance or extended-dominance due to the comparison of costs and QALYs. These would be the only three treatments optimally available to maximize cost-effectiveness for PsA in TNF-alpha experience patients. Other treatments would not provide optimal health benefits or optimal cost savings in comparison.

The value-based price analysis and sensitivity analyses further underline the results that BKZ does not end up on the cost-effectiveness frontier. From the FSS, the average BKZ contract price per pack (2 doses) is $10,779.02. At the $100,000/QALY ICER threshold, the contract price should be nearly halved to $5,872.87. However, at higher thresholds through the sensitivity analysis, the contract price moves much closer to the FSS-derived price. At $150,000/QALY the pack price becomes $8,240.79. At $200,000/QALY, the pack price of $10,608.71 becomes very close to the FSS contract price of $10,779.02. The sensitivity analysis suggests further discounts from the FSS contract price to move BKZ to be more cost-effective as an optimal treatment on the cost-effectiveness frontier. The current manufacturer list price for BKZ is $7,200 per syringe which multiplies to $14,200 per pack (UCB, 2023).

Chapter 7

Conclusions

The initial results that this thesis supports underline a larger shift in the United States healthcare system towards a more evidence-based approach for supporting drug price negotiations using cost-effectiveness analysis. Compared to countries outside the United States, other HTA agencies are more integrated into the pricing systems and provide greater scrutiny on pricing with consideration to the value added to society by a particular drug. The United States' primary pricing watchdog, ICER, is now gaining more traction to support federal negotiations for Medicare drug pricing with the passage of the Inflation Reduction Act (IRA) in 2022. The IRA ushers in a system where the Centers for Medicare & Medicaid Services (CMS) now directly negotiate with drug companies for costly "single-source brand-name Medicare Part B and Part D drugs" (CMS, 2023). Negotiations allow manufacturers to submit evidence to justify a higher price after CMS proposes a price based on a cost-effectiveness analysis likely of similar style to ICER. This pricing structure has also included patient-focused listening sessions, public information submissions, and comments from manufacturers regarding information to support different prices.

Ultimately, this thesis determines that bimekizumab is not cost-effective against all currently available drugs to treat PsA. Following a social welfare-focused model of evaluating overall health benefit to costs, prescribing bimekizumab would not result in net health benefit due to larger health insurance premiums and individuals falling out from insurance coverage.

Inflation Reduction Act Implications

The IRA negotiation structure requires manufacturers to submit R&D costs, production and distribution costs, federal financial support, pending and approved patents, and market data on revenue and sales volume (CMS, 2023). It also requires effectiveness evidence on the extent of the drug's benefit

over alternatives, prescribing information, comparative effectiveness of the drug and comparators, and the degree of meeting unmet medical needs). The language on the extent of the drug's added benefit is very reminiscent of the IQWiG style of HTA in Germany; however, the U.S. legally excludes content of QALYs. Seeking the compute a "maximum fair price" (MFP), CMS will set a MFP ceiling as the lowest of average net negotiated price for a Part D drug, average sales price for a Part B drug, or percent of average non-federal average manufacturer price depending on time since FDA approval. CMS's initial offer will be below the MFP ceiling by evaluating indications for the drug and comparable alternatives combined with Part D net price or average sales price as a starting point reminiscent of IQWiG. They will ultimately use a qualitative approach to "preserve flexibility in negotiation including the ability to consider nuanced differences" which leads to possible adjustments in the CMS offered price and counteroffers.

ICER's influence in the negotiation framework is significant if not explicitly outlined in the legislation. ICER published a special report to inform CMS negotiations on selected drugs Eliquis and Xarelto which follow a similar analysis structure to this thesis. This ICER-style U.S.-focused evaluation of bimekizumab in this thesis underlines different results from the primary framework by Sigurdardottir et al. (2023) published in Sweden. The U.S.-model maintains a different pricing structure based on the averages from Medicare claims data. Additionally, the U.S. model makes strong health assumptions in order to best follow the Sigurdardottir et al. (2023) model without access to its data. Such assumptions can significantly alter the QALY metric and thus impact the ICER ratios and BKZ's cost-effectiveness.

Limitations and Shortcomings

One of the primary limitations of this thesis is the inability to access to original Swedish model from Sigurdardottir et al. (2023). Without this data, the model in this thesis tries to best replicate this process without knowing all of the assumptions made that led to the published results. Additionally, some

data was difficult to replicate from the Swedish study, such as shifting from a Swedish health value set to one for the United States. Instead, strong assumptions were made in place of this difficulty in that the Swedish and U.S. value sets showed similar results. The Markov model is limited in its own process through assumed independence of ACR and PASI measures which is not realistic compared to health outcomes in reality. Additionally, generalizations about heath progressions in PASI, HAQ-DI, and EQ-5D are a weak point due to the difficulty to model health in reality.

A further limitation of this research is the strength of its application in the United States. The U.S. outlaws use of the QALY in health valuation due to discriminatory concerns about older individuals and those suffering from conditions having undervalued years of health. This research provides a valuable insight to the pricing process and cost-effectiveness of bringing a new drug on the market, but is currently limited to influence as opposed to direct application. Additionally, the CMS pricing methodology remains confidential but appears that it follows a cost-effectiveness approach. However, the use of this analysis extends beyond the strict cost per QALY that the ICER ratio suggests. This analysis is valuable as information that can assist in the computation of a maximum fair price in the Medicare negotiation structure. The analysis and sensitivity testing can also prove beneficial as watchdog suggestions for manufacturers to deliver better cost-effectiveness and market access from U.S. payers. With a more cost-effective intervention, they could see greater market access as a viable alternative to other drugs available for any given treatment.

Final Conclusions

This thesis has served to be an extremely valuable experience into the workings of drug pricing and determining the value of clinical treatments. Without the connection of clinical data and cost to the patient journey, price setting can quickly fall short of maximizing the limited resources of the healthcare system. The U.S. poses a unique challenge with its complicated healthcare system as compared with those

around the world, however, it faces the same underlying economic principle of how to maximize limited resources and opportunity costs. There is no one uniform way to evaluate a drug, but many different ways and models help to provide critical information to those who are considering how to set prices for the public and private sectors. With ongoing Medicare negotiations, the U.S. system is placing more weight on this evaluation of the added value drugs bring to society considering their costs. Research such as ICER ratio analysis and value based pricing play a strong role in this process while not being the ultimate decision-making factor. Ultimately, new drugs provide innovation to the healthcare system but it is crucial to consider they may not always deliver net benefit to society at their list prices.

Appendix A

Glossary

ACR## – American College of Rheumatology % joint symptom improvement

BKZ – Bimekizumab

CADTH – Canadian Agency for Drugs and Technologies in Health

CASPAR – Classification Criteria for Psoriatic Arthritis

CEA – Cost-Effectiveness Analysis

CMS – Centers for Medicare and Medicaid Services

CZP – Certolizumab Pegol

DMARDs – Disease-modifying Anti-rheumatic Drugs

- csDMARDs – Conventional Disease-modifying Anti-rheumatic Drugs
- ts/bDMARDs – Targeted Synthetic Biologic Disease-modifying Anti-rheumatic Drugs

EQ-5D – EuroQol 5 Dimensions

FSS – Federal Supply Schedule

HAQ-DI – Health Assessment Questionnaire - Disability Index

HTA – Health Technology Assessment

HBPB – Health-Benefit Price Benchmark

ICER organization – Institute for Clinical and Economic Review

ICER ratio – Incremental Cost-Effectiveness Ratio

Intervention – A healthcare treatment such as a pharmaceutical drug or other health technology

IRA – Inflation Reduction Act

ISPOR – Professional Society for Health Economics and Outcomes Research

IQWiG – Institute for Quality and Efficiency in Health Care

IXE – Ixekizumab

MDA – Minimal Disease Activity

NICE – National Institute for Health and Care Excellence

NSAIDs – Non-steroidal Anti-inflammatory Drugs

PASI## – Psoriasis Area and Severity Index % skin symptom improvement

PsA – Psoriatic Arthritis

QALY – Quality Adjusted Life Year

RCTs – Randomized Control Trials

TNFi-exp – Tumor Necrosis Factor inhibitor-experienced

UPA – Upadacitinib

UST_90 – Ustekinumab 90mg

WAC – Wholesale Acquisition Cost

Appendix B

Systematic Review Selections

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Appendix C

Model Cost Inputs

Cost inputs mirror Sigurdardottir (2023) and are updated to USD using average contract price across all formulations from the Department of Veterans' Affairs Federal Supply Schedule (FSS).

Treatment	Formulation	Dose per formulation	Posology	Price per pack ($)	Price per vial/tablet ($)	Doses per annum year 1	Doses per annum year 2	Cost per annum year 1 ($)	Cost per annum year 2 ($)
Bimekizumab 160 mg	Pre-filled syringe	160.0 mg	Q4W	10,779.02	5389.51	13.04	13.04	70,279	70,279
Certolizumab pegol 400 mg induction and 200 mg maintenance	Pre-filled syringe	200.0 mg	Induction dosing: 400 mg at 0, 2, and 4 weeks. Maintenance dosing: 200 mg Q2W	4235.9	2117.95	29.57	26.09	62,628	55,257
Ixekizumab 1 induction dose schedule	Pre-filled syringe	80.0 mg	Initially 160 mg for 1 dose, then maintenance 80 mg Q4W, consider discontinuation of treatment if no response after 16–20 weeks	5192.02	5192.02	14.78	13.04	76,738	67,704
Ustekinumab 90 mg	Pre-filled syringe	90 mg	Induction dosing: 90mg (body weight > 100 kg) at 0 and 4 weeks. Maintenance dosing: 90 mg (body weight > 100 kg) every 12 weeks	13,867.24	13,867.24	8.00	4.35	110,938	60,322
Upadacitinib 15 mg	Per tablet	15.0 mg	15 mg once daily	4,371.19	145.71	365.25	365.25	53,219	53,219
Methotrexate (csDMARDs)	Per tablet	2.5 mg	Induction dosing: 15 mg weekly for 1 month. Maintenance dosing (minimum maintenance dosing assumed): 15 mg weekly	22.5483	0.55	312.86	312.86	171.66	171.66

Appendix D

Model Health Inputs

Health inputs are derived from Sigurdardottir et al. (2023), Merola et al. (2023), or are updated using thesis methodology.

	csDMARDs	UST_90	IXE	UPA	BKZ	CZP
p_ACR50	0.07	0.19	0.39	0.41	0.46	0.71
p_PASI50	0.21	0.91	0.72	0.58	0.84	0.83
p_PASI75	0.13	0.84	0.59	0.45	0.74	0.73
p_PASI90	0.06	0.73	0.45	0.31	0.61	0.59

rr_death	Relative Risk of Death	1.05
p_discontinue	Probability to Discontinue Treatment	0.2596
HAQ_0	Baseline HAQ-DI	0.99
dHAQ16_ACR50	Change in HAQ-DI for ACR50	-0.567
dHAQ16_ACRLT50	Change in HAQ-DI for ACRLT50	-0.225
PASI_LT8	PASI <8 value	3.2
PASI_8_12	PASI 8-12 value	9.7
PASI_GT12	PASI >12 value	20.5
p_PASI_LT8	Probability of PASI <8	0.708
p_PASI_8_12	Probability of PASI 8-12	0.128
p_PASI_GT12	Probability of PASI >12	0.164
PASI_0	Baseline PASI	6.8692
HAQ_progress	Annual HAQ-DI score progression	0.025
r_discount	Discount rate (Costs and Outcomes)	0.03
EQ-5D Int	EQ-5D Intercept	2.361
HAQ-DI Coeff	HAQ-DI Coefficient	-0.821
PASI Coeff	PASI Coefficient	-0.03
HAQ-DI*PASI Coeff	HAQ-DI*PASI Coefficient	0.017
Sex Coeff	Sex Coefficient	-0.095
p_female	Probability of Female	0.525
p_male	Probability of Male	0.475

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ACADEMIC VITA

Derek Deihl
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EDUCATION

The Pennsylvania State University — **University Park, PA**
Smeal College of Business, Schreyer Honors College — *May 2024*
Bachelor of Science in Finance
Bachelor of Science in Economics

EXPERIENCE

Johnson & Johnson — *June 2023 – August 2023*
Finance Intern – Compliance Audit & Investigations — *New Brunswick, NJ*

- Investigated travel & expense issues and conflicts of interest through expense analysis and online research to provide relevant evidence and information for sensitive issue reports
- Led team analysis and presentation on physical and mental well-being to Global Audit senior leadership team
- Refreshed new-hire Microsoft Planner to streamline onboarding experience and created Microsoft Form for process feedback
- Enhanced understanding of Finance audits, FCPA audits, and risk-based reviews

Novartis — *June 2022 – August 2022*
Finance Intern – Government Pricing & Reporting — *East Hanover, NJ*

- Disrupted authorized generic shipment processes through automation to deliver 75% increase in efficiency
- Led team analysis and presentation on market outlook and employer attractiveness to Finance executive leadership
- Designed and implemented creative team planner encompassing all monthly, quarterly, and annual pricing activities to structure team meetings and optimize timeline of agenda items
- Increased knowledge of divested products, RPU analysis, 340B/PHS entities, price restatements, and reconciliations
- Restructured and updated job aids for all price types and activities to significantly streamline role changes and onboarding

Penn State Finance Department — *January 2022 – May 2024*
Lead Teaching Assistant – Corporate Finance — *University Park, PA*

- Directed group of five teaching assistants to deliver new course content, class coverage, office hours, and grades
- Tutored students to solidify course concepts, Excel skills, mathematical calculations, and financial calculator use
- Delivered fellowship research program cataloging success of honors introductory finance alumni over 20+ years

LEADERSHIP

Penn State Marching Blue Band — *March 2022 – March 2024*
Secretary, Saxophone Section Leader

- Constructed and facilitated $30,000+ of merchandise acquisitions and distribution to 300+ band members
- Created and maintained attendance system, membership records, officer board meeting minutes, and travel logistics
- Trained and evaluated new members' marching and performing technique to support and raise organization standards

Tariff Center Integrity Advocates — *November 2020 – May 2024*
Stakeholder Engagement Lead

- Engaged in monthly strategic planning focus groups to pilot, develop, and roll out the Smeal Ethical Leadership Challenge (SELC) for 3,000+ students
- Organized the First-Year Business Student Honor & Integrity Case Competition to drive the criticality of honor and integrity in both academics and future business careers
- Managed scheduling and volunteering at Smeal Involvement Fairs and Accepted Students Programs to ensure a presence for the organization and its values
- Drove accountability for honor and integrity in the Penn State student body through various promotional efforts

SKILLS / INTERESTS

- Finance and Economics Honors Thesis: Pharmaceutical Value-Based Pricing and Cost-Effectiveness
- Grader for ECON 444 – Economics of the Corporation
- Proficient in Tellius, Minitab, Model N, iMany; Basic in Power BI, Tableau, Stata, R
- Application of the Enneagram of personality types to optimize teamwork and enhance individual/group interactions
- Volunteering in various music venues including high school band programs and LIONS Club
- Penn State Blue Band, Athletic Pep Bands, and Jazz Ensembles

HONORS / AWARDS

- Student Marshal for Finance Major
- Robert W. "Bear" Koehler Award for Distinguished Service
- Academic Excellence Scholarship
- Chapel Executive Internship Program
- D'Ambrosio Honors Scholarship
- Department of Economics Undergraduate Award
- Eagle Scout