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# Budget impact analysis of upadacitinib for the management of moderate-to-severe atopic dermatitis in patients treated with systemic therapies in the United States

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# BUDGET IMPACT ANALYSIS OF UPADACITINIB FOR THE MANAGEMENT OF MODERATE-TO-SEVERE ATOPIC DERMATITIS IN PATIENTS TREATED WITH SYSTEMIC THERAPIES IN THE UNITED STATES

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science

at Virginia Commonwealth University

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| **AAAAI** | American Academy of Allergy, Asthma, & Immunology |
| **AAD** | American Academy of Dermatology |
| **AD** | Atopic Dermatitis |
| **AWPs** | Average Wholesale Prices |
| **BUN** | Blood Urea Nitrogen |
| **CBC** | Complete Blood Count |
| **CEA** | Cost-effectiveness analysis |
| **CI** | Confidence Intervals |
| **CLFS** | Clinical Laboratory Fee Schedule |
| **CPI** | Consumer Price Index |
| **CPT** | Current Procedural Terminology |
| **EASI** | Eczema Area and Severity Index |
| **EC** | European Commission |
| **FDA** | Food and Drug Administration |
| **FLG** | Filaggrin Gene |
| **HBPB** | Health-Benefit Price Benchmarks |
| **ICER** | Institution for Clinical and Economic Review |
| **Ig** | Immunoglobulin |
| **IL** | Interleukin |
| **ISPOR** | International Society for Pharmacoeconomics and Outcomes Research |
| **JAK** | Janus Kinase |
| **K** | Potassium |

| | |
|---|---|
| **Kg** | Kilograms |
| **Mg** | Magnesium |
| **Mg** | Milligram |
| **ML** | Milliliter |
| **nbUVB** | Narrow Band Ultraviolet-B |
| **OTC** | Over the Counter |
| **PMPM** | Per Member Per Month |
| **PMPY** | Per Member Per Year |
| **POEM** | Patient-Oriented Eczema Measure |
| **PTMPM** | Per Treated Member Per Month |
| **QALY** | Quality-adjusted life year |
| **QoL** | Quality of Life |
| **SC** | Subcutaneous |
| **SCORAD** | SCORing Atopic Dermatitis |
| **TCIs** | Topical Calcineurin Inhibitors |
| **TCSs** | Topical Corticosteroids |
| **TMR** | Transparency Market Research |
| **US** | United States |
| **WACs** | Wholesale Acquisition Costs |

## ABSTRACT

## BUDGET IMPACT ANALYSIS OF UPADACITINIB FOR THE MANAGEMENT OF MODERATE-TO-SEVERE ATOPIC DERMATITIS IN PATIENTS TREATED WITH SYSTEMIC THERAPIES IN THE UNITED STATES

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science at Virginia Commonwealth University.

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**Objective:** This study evaluated the budget impact of introducing upadacitinib for patients with uncontrolled moderate-to-severe atopic dermatitis (AD) from a United States (U.S.) private payer perspective.

**Methods**: The model estimated costs before and after the adoption of upadacitinib for a hypothetical one million covered lives over 3 years. The model included immunosuppressant agents and dupilumab. Market uptake was assumed to be 2% per year. Treatments incur a cost for drug acquisition, and the costs associated with drug administration, laboratory testing, and clinic visits. The model calculated the impact on the budget in 2022 U.S. dollars. Various assumptions on market uptake were analyzed, and a sensitivity analysis was performed.

**Results**: For one million covered lives with an estimated 3607 people receiving immunosuppressant agents or dupilumab, the total cost after introducing upadacitinib increased by $3.5, $7.0, and $10.5 million in years 1–3, respectively, resulting in a cumulative increase of $21.1 million over 3 years. The incremental per member per year costs were $3.52, $7.04, and

$10.59 in years 1–3, respectively, resulting in an increase in per member per month costs of $0.29 in year 1, $0.59 in year 2, and $0.88 in year 3. The incremental per treated member per month costs were $70.77, $140.72, and $210.67 in years 1–3, respectively. Scenario and sensitivity analyses confirmed the model robustness.

**Conclusions**: The introduction of upadacitinib had a high impact on the U.S. private payer budget. The use of upadacitinib may increase the cost of treating patients with uncontrolled moderate-to-severe AD.

## CHAPTER 1. INTRODUCTION AND BACKGROUND

Atopic dermatitis (AD), also known as eczema, is a chronic or relapsing inflammatory skin disease.[1] It is characterized by skin barrier disruption and immune dysregulation largely mediated by type 2 helper T cells.[1] An AD-affected individual may suffer from skin irritation, inflammation, and pruritus, and the disease typically has flares and remissions that occur intermittently, often for unexplained reasons.[2] AD is a multifactorial disease that is influenced by genetics, immune, and environmental factors.[3] There is controversy over whether AD is predominantly caused by barrier dysfunction (outside–in hypothesis) or by an inflammatory response to environmental allergens and irritants (inside–out hypothesis).[4] The "outside-in" hypothesis suggests that AD is preceded by impaired epidermal barrier function and thus requires it for disease to manifest.[5] Filaggrin gene (FLG) mutations that result in loss-of-function are indicative of this hypothesis.[5] The FLG gene dysfunction can lead to poor epidermal barrier function, which increases water loss and makes the skin more prone to foreign substances that could result in inflammation in the skin and systemically, and thus, can lead to atopic diseases, for example, asthma and food allergy.[5] The "inside-out" hypothesis implies that inflammation occurs before and even contributes to AD barrier dysfunction.[6] This hypothesis implies that AD might be linked to variants in genes primarily involved in immune pathways, such as interleukin (IL)-4R, IL-18, and IL-31.[6] It also has been suggested that environmental exposures may trigger and/or flare AD disease among predisposed individuals.[3] Different environmental factors play an interdependent role in AD disease, including individual usage of personal care products and exposure to climate, pollution, and food.[3]

AD most often starts in childhood; more often than not, it occurs between 3 and 6 months, though it may occur at any age.[7] The risk of developing AD is much higher in those who

have a family or personal history of other atopic disorders such as asthma or allergic rhinitis.[8] Because of the chronic nature of this disease, as well as its relapsing nature, it can be associated with a substantial or multidimensional patient burden.[9] This is especially true in moderate-to-severe patients, who may have increased atopic comorbidities (asthma, nasal, and food allergies[10]), neuropsychiatric conditions (sleep disturbance[11], anxiety, and depression[12]), and impaired quality of life (QoL).[13] Furthermore, moderate-to-severe AD patients with inadequate disease control report even higher patient-reported burden, including anxiety, depression, sleep disturbance, and impaired QoL, than patients with controlled disease.[14]

In the United States (U.S.), it is estimated that the prevalence of AD is 10.7% among children under 18 years of age and 7.3% among adults.[15,16] Although AD is often considered a childhood disease, recent evidence suggests that it is more common in adults than previously recognized.[17] According to a recent population-based estimate for adults, a total of 16.5 million have AD in the U.S., of which 6.6 million (40%) report moderate-to-severe symptoms.[16] The prevalence of AD in adult females (11.1%) is higher than males (9.1%),[18] and the prevalence of AD in African American children (19.3%) is higher than European American children (16.1%).[19]

Currently, there is no consensus regarding the diagnostic testing that should be performed on AD patients.[20] Diagnostic approaches for AD vary widely due to the lack of reliable biomarkers that can distinguish AD from other skin diseases.[20] Therefore, the diagnosis for AD is based on a constellation of clinical features, morphology, and distribution of skin lesions, and associated clinical signs and symptoms.[20] In some cases, skin biopsy specimens or other tests, including total and/or allergen-specific serum Immunoglobulin (Ig)E, and/or genetic tests, may help to rule out other skin conditions.[20]

The AD severity assessment helps guide clinical decision-making and is evaluated in clinical trials by various tools including, the Eczema Area and Severity Index (EASI) score, the SCORing AD (SCORAD) index, and the Patient-Oriented Eczema Measure (POEM) severity score.[20,21] The EASI score is a simple tool that measures the extent (area) and severity of AD.[22] In EASI scoring, patients are categorized as follows: 0 = clear; 0.1-1.0 = almost clear; 1.1-7.0 = mild; 7.1-21.0 = moderate; 21.1-50.0 = severe; 50.1-72.0 = very severe.[22] The SCORAD index is a clinical tool used to assess AD severity based on area affected, intensity (redness, swelling, oozing, scratch marks, skin thickening, and dryness), and subjective symptoms (itchiness and sleeplessness).[23] Based on the SCORAD index, the severity of AD can be classified into mild (<15), moderate (between 15 and 40), and severe (≥40).[24] The POEM scale is a tool used to monitor AD severity by evaluating whether time spent with AD symptoms (itching, bleeding, flaking, weeping or oozing clear fluid, cracked skin, dry skin) interferes with sleep during the past week.[25] The POEM scores are categorized into five severity bands as follows: POEM scores of 0–2 = clear/almost clear; 3–7 = mild; 8–16 = moderate; 17–24 = severe; 25–28 = very severe AD.[25] American Academy of Dermatology (AAD) guidelines do not recommend the use of disease severity scales for clinical practice and suggest only that they be used in clinical trials.[20] In clinical practice, they recommend that severity of AD be classified according to a patient's physical symptoms, the amount of body surface area affected, the location of the rash, and the condition's impact on sleep and QoL.[26] If the patient has not responded to treatment, then the AD severity assessment should be re-evaluated.[20]

AD is an incurable condition. The treatment focuses on reducing the number of exacerbations or flares, as well as the duration and severity of flares if they do occur, improving the skin's barrier function, suppressing inflammation, and relieving pruritus.[27] All AD patients,

regardless of the severity of their disease, should follow a routine of proper skin care, moisturizers, antiseptic measures, and avoiding triggers at all times.[28] Patients who can be controlled with non-pharmacological management often have mild disease, whereas when their symptoms cannot be adequately controlled with non-pharmacological therapies, they are considered to have moderate-to-severe disease.[28] The AAD[29] and the American Academy of Allergy, Asthma, & Immunology (AAAAI)[30] recommend the use of proactive maintenance topical anti-inflammatory medications such as topical corticosteroids (TCSs) or topical calcineurin inhibitors (TCIs) as an additional treatments to the non-pharmacological management for moderate-to-severe AD patients. For acute treatment of flares in moderate-to-severe AD patients, TCSs or TCIs have to be applied consistently in flare-prone areas and at the first sign of a flare.[29] Acute flares for moderate-to-severe AD patients may be treated with medium potency or low potency TCSs based on patients' and providers' preferences.[29] TCSs have been used for more than 60 years to treat AD, as both an active inflammatory disease as well as a prevention of relapse, except on areas of thin or sensitive skin.[29] However, treatment adherence concerns with the use of TCSs can be negatively impacted by the fear of TCSs withdrawal and side effects.[31,32] TCIs, tacrolimus ointment and pimecrolimus cream, are newer formulations that are effective for both chronic inflammation and acute flare-ups of AD, and they have particular use on thin or sensitive skin sites.[29,33] Despite this, there are a number of adverse reactions associated with TCIs use, including transient burning sensations, pruritus, and erythema.[34] Additionally, TCIs carry a "black box" warning that indicates a potential risk of malignancy, though many clinical experts question the validity of the warning.[35] Crisaborole 2% ointment is an anti-inflammatory non-steroidal topical treatment option for AD patients with mild to moderate disease.[36] Although crisaborole 2% is considered safe, burning/stinging can occur at or near the application site.[36]

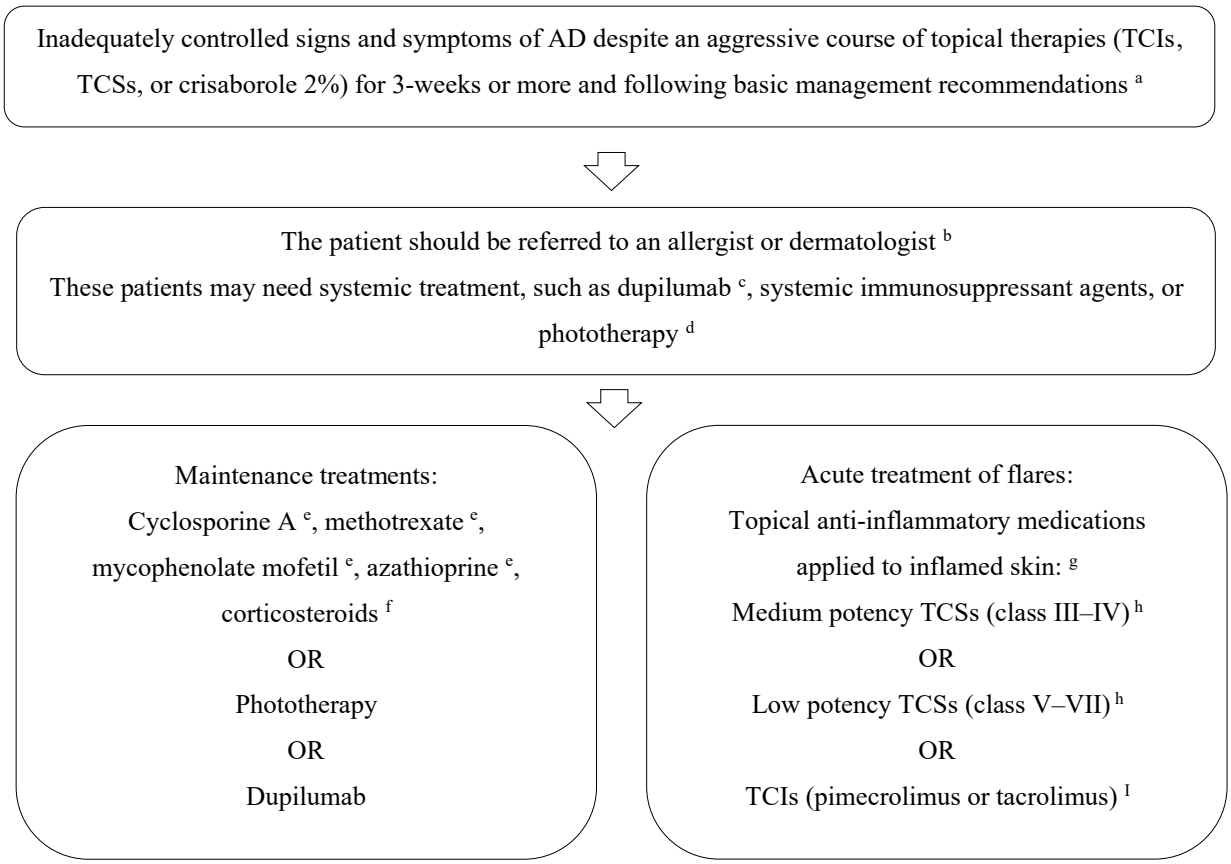
Patients with moderate-to-severe disease who do not respond to the maintenance topical anti-inflammatory medications may benefit from second-line treatments such as phototherapy or systemic medications.[37] Prior to starting the second-line treatment, it is important to assess these patients for nonadherence, comorbidity, and other factors that might negatively influence the response to previous therapy.[38] In adults with recalcitrant eczema, narrow band Ultraviolet-B (nbUVB) phototherapy can be particularly beneficial for treating widespread eczema.[39] The nbUVB penetrates the skin and affects the immune system by reducing inflammation.[39] Phototherapy, however, leads to premature aging of the skin and increases the risk of skin cancer overtime, and for this reason, it is suggested to be used cautiously.[39] In terms of cost, convenience, and accessibility, the patient should be willing and able to commit to phototherapy.[38] Treatment with systemic immunosuppressant agents, such as corticosteroids, azathioprine, methotrexate, mycophenolate mofetil, and cyclosporine A, are indicated for very severe, chronic, relapsing AD in patients whose optimized topical anti-inflammatory regimens do not provide adequate relief from symptoms.[39] Such treatments are off-label in the U.S. and generally limited for patients with moderate-to-severe AD who do not respond to topical anti-inflammatory medications.[39] Efficacy and safety of these treatments are limited, and there are few studies in the literature that compare them to one another.[39] According to the AAD guidelines, systemic corticosteroids, such as prednisone, should be avoided if possible for the treatment of moderate-to-severe AD, and maintenance treatment with oral corticosteroids is not recommended for serious AD.[39] These drugs should be reserved exclusively for treating acute, severe exacerbations and for transitioning to other systemic, steroid-free therapies.[39] Patients with AD may be treated with oral antihistamines to reduce pruritus and improve their QoL, but there is insufficient evidence to recommend general use of antihistamines as a treatment

approach.[39,40] There are several serious side effects associated with systemic immunosuppressants, including increased risk of infections, increased risk for certain types of cancers, increased risk of kidney damage with cyclosporine A and methotrexate, increased blood pressure with cyclosporine A and corticosteroids.[39,41] As of that, they require close initial laboratory testing and/or ongoing laboratory monitoring.[39,41] Current guidelines discourage general use of systemic immunosuppressant agents including oral corticosteroids.[30,39]

Yet, while most patients are able to improve their symptoms or control them with traditional treatments, some do experience treatment failure, including a decrease in QoL, inadequate clinical improvement, or failure to achieve long-term control.[42] AD has been shown to affect the U.S. economy in many ways. A conservative estimate of the economic cost of AD, including direct medical costs, indirect costs from lost productivity, and QoL impacts, is $5.3 billion annually in 2015.[43] Evidence from the 2013 U.S. National Health and Wellness Survey indicates that the annual per patient total direct, emergency department visits, hospitalization, healthcare provider visits costs for AD patients are significantly higher than their non-AD counterparts.[10] AD patients have higher out-of-pocket health care costs than those without the disease, and the out-of-pocket health care costs for AD per person per year ($371-$489) was higher than the out-of-pocket costs for hypertension ($206-$241) and diabetes mellitus ($353-$210).[44] Patients with AD disease have a considerably higher absenteeism and activity impairment rate compared to those without.[45] In some cases, disease flares can impact 15% of a workday of those who have the disease, which incur a considerable indirect medical cost.[46] Approximately 55% of adults with AD report inadequate disease control.[14] This suggests the need for better treatment options for AD patients, especially those suffering with uncontrolled moderate-to-severe symptoms.

In light of this significant economic impact, the number of options for treating moderate-to-severe AD patients with uncontrolled symptoms has resulted in the approval of several new classes of medications for those patients.[47] As of March 2017, the U.S. Food and Drug Administration (FDA) approved dupilumab, a human monoclonal IgG4 antibody, for the treatment of patients aged 6 years and older with moderate-to-severe AD.[48] The approval was for use in uncontrolled AD or when other therapies are not advisable, becoming the first biologic agent registered for the treatment of this chronic skin condition.[48] Dupilumab can be used with or without TCSs or TCIs for moderate-to-severe AD patients with inadequate response.[49] IL-4 receptor-a is targeted by dupilumab, effectively inhibiting the signaling of IL-4 and IL-13, which reduces symptoms and signs of this diseases.[49,50] Dupilumab is licensed in the U.S. for subcutaneous (SC) administration, and so far, it is considered a safe treatment option for moderate-to-severe AD who do not respond to topical anti-inflammatory medications.[51] Dupilumab has no recognized short term or serious side effects including injection site reactions and eyelid inflammation. Thus, it does not require initial laboratory testing or ongoing laboratory monitoring.[51] In spite of dupilumab 's novel therapeutic approach, it may not be appropriate for all patients with AD because of the SC administration and the unique immunophenotype of AD disease.[52] Therefore, there is a need for a broader range of treatment options for this condition, particularly oral medications, that can provide improved clinical responses for moderate-to-severe AD patients with inadequate response. Figure 1 presents a summary of patient profiles and current treatment options for the moderate-to-severe atopic dermatitis patients with inadequate response to topical anti-inflammatory medications.

Figure 1. Patient Profiles and Recommendations for the Treatment of Moderate-to-Severe Atopic Dermatitis Patients with Inadequate Response to Topical Medications[53]




*AD, atopic dermatitis; TCIs, topical calcineurin inhibitors; TCSs, topical corticosteroids*

[a] Basic management includes skin care and antiseptic measures, trigger avoidance, and, specifically, when the condition significantly impacts daily activities, psychological health, and quality of life.[38]

[b] It is important to evaluate the patient for nonadherence, comorbidity, and other factors that might negatively affect response of previous therapy.[38]

[c] Indicated for patients aged 6 years and older with moderate-to-severe AD whose disease is not adequately controlled with topical anti-inflammatory medications or when those therapies are not advisable.[48]

[d] Beneficial for treating widespread eczema.[39]

[e] Not approved by the Food and Drug Administration to treat moderate-to-severe AD.[39]

[f] Approved by the Food and Drug Administration to treat AD, but not recommended for long-term maintenance.[39]

[g] Useful for flares (depending on severity of the flare and provider/patient's preference; not indicated dosage).[39]

[h] Except for face and/or eyes.[39]

[I] Include face and/or eyes.[39]

There are currently other biologic therapies being developed for treating AD, including omalizumab, lebrikizumab, and tralokinumab.[54] Unlike antibody-based therapies, which are usually targeting cytokines or their receptors, small molecules are newer therapies being developed to interfere with intracellular signaling pathways.[54] Janus kinase (JAK) inhibitors constitute the largest group of these molecules.[54] Oral JAK inhibitors, such as upadacitinib, baricitinib, and apremilast, could provide effective treatment option for moderate-to-severe AD given their rapid onset of action.[54] As of January 2022, The U.S. FDA approved upadacitinib for the treatment of moderate-to-severe AD in adults and children 12 years of age and older whose disease did not respond to previous treatment and is not well controlled with other pills or injections, including biologic medications, or when use of other pills or injections is not recommended.[55] Upadacitinib is currently approved by the European Commission (EC) for the treatment of moderate-to-severe AD in patients who are candidates for systemic therapy.[56] Upadacitinib is a selective JAK inhibitor, which is designed to have increased selectivity for JAK1 over JAK2, JAK3, and tyrosine kinase 2.[57] Upadacitinib side effect profile indicates that infections are more common and certain laboratory parameters are altered during treatment, including elevated liver function values, blood count changes, and elevated creatine kinase values, and thus, this treatment requires more intensive patient monitoring.[58] In addition, a black box warning has been added by the FDA on all approved JAK inhibitors in September 2021 regarding serious heart-related events such as heart attack, stroke, cancer, blood clots, and death.[59] Several randomized-controlled trials showed that upadacitinib (once-daily/15 or 30 mg) is a well-tolerated and effective treatment option for patients with moderate-to-severe AD.[60,61] In addition, a recent randomized-controlled trial showed that upadacitinib (30 mg once daily, orally) is well tolerated and is more effective than dupilumab (300 mg every other week, SC) for

moderate-to-severe AD adult patients after 16 weeks of treatment.[62] Therefore, upadacitinib could offer a viable treatment alternative to current systemic therapies for adult patients with moderate-to-severe AD who do not respond to topical anti-inflammatory medications.

Since treating moderate-to-severe AD patients can be costly, researchers have been performing economic evaluations of these breakthrough treatments with the current or standard of care.[63–65] In August 2021, the Institution for Clinical and Economic Review (ICER) published a report evaluating the clinical effectiveness and value of new therapies indicated for AD, including upadacitinib.[65] By performing a cost-effectiveness analysis (CEA) comparing upadacitinib for moderate-to-severe AD to the standard of care (topical medications) and dupilumab, over a five-year time horizon, the incremental CEA base case results were $1,912,200 per quality-adjusted life year (QALY) for upadacitinib and dupilumab, and $248,400 per QALY for upadacitinib and the standard of care. The report also stated that the estimated health-benefit price benchmark (HBPB), a commonly cited cost-effectiveness threshold between $100,000 and $150,000 per QALY gained, is $30,400-$41,500 per year for upadacitinib, which would require a 35-53% discount off the treatment's current U.S. list price of $64,300 to reach common threshold of cost-effectiveness.[65]

To this direction, the concept of budget impact analysis can be of significant benefit as payers are still struggling to deal with the escalating cost of new treatments to treat patients with uncontrolled moderate-to-severe AD.[38] In addition, there is also no certainty about how the adoption of upadacitinib will affect formulary budgets for U.S. private payers. The objective of this study is to estimate the incremental budgetary impact of the introduction of upadacitinib for patients with moderate-to-severe AD whose disease is not adequately controlled with topical anti-inflammatory medications from a U.S. private payer perspective.

# CHAPTER 2. METHODS

## 2.1 Model Structure

A flexible budget impact model based on Microsoft Excel was developed from a U.S. private payer perspective to estimate the expected costs to be incurred by the payer of introducing upadacitinib over a 3-year time horizon. Because of the perspective of the model, it does not account for the cost of non-insured moderate-to-severe AD patients.

The model started with a hypothetical one million covered lives and then estimated the number of eligible patients for upadacitinib using publicly available data. The treated population size remained constant each year for the model estimate. Moderate-to-severe AD patients whom are eligible for upadacitinib were divided into subgroups based on the current systemic treatment options available in the AAD[39] & AAAAI[30] guidelines, which include immunosuppressant agents (cyclosporine A, methotrexate, mycophenolate mofetil, and azathioprine), and the only FDA-approved biological therapy (dupilumab). Despite the FDA's approval for oral corticosteroids, they are not recommended for patients with moderate-to-severe AD who need long-term maintenance treatment, so they were not included in the model.[29] We thereafter estimated the annual number of patients treated with each immunosuppressant agent and dupilumab, as well as the number of patients new to treatment each year. We estimated the annual number of patients who receive upadacitinib according to the annual market uptake and the market shares of available treatment options. The current market shares were based on different market estimates for each immunosuppressant agent and dupilumab. Data on immunosuppressant market shares are not available publicly. For our estimation, however, a study that analyzed retrospective claims data regarding the treatment patterns among patients with AD in the U.S. was used.[66] The study was conducted using the IQVIA Health Plan Claims

that includes patients who newly initiated a treatment for moderate-to-severe AD.[66] The vast majority of patients were 18 years of age or older and commercially insured.[66] The market share for dupilumab was estimated using a report published by the Transparency Market Research (TMR) regarding key market dynamics and the exponential growth of biological drugs for AD.[67]

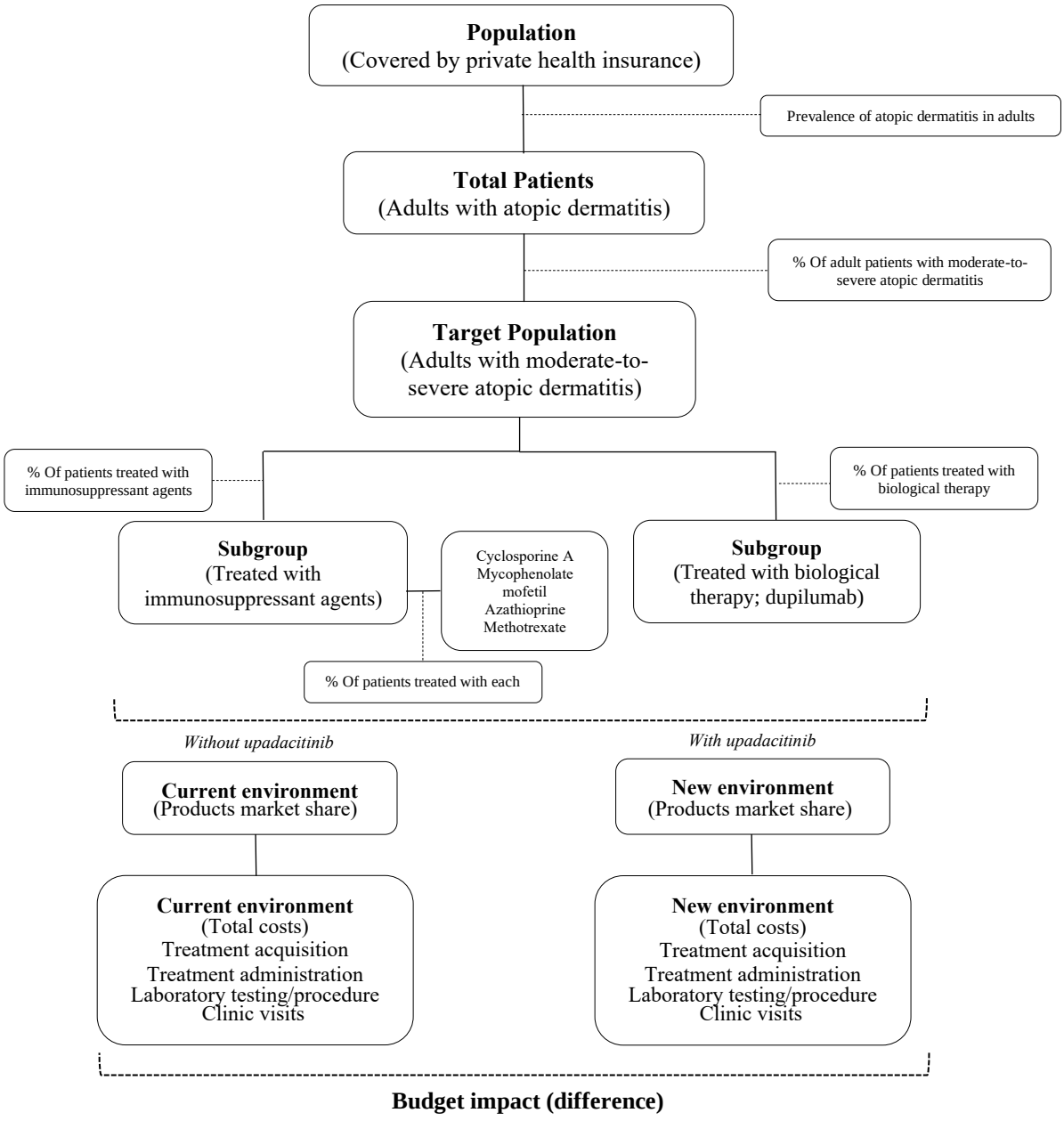
To estimate the budget impact of adding upadacitinib to the treatment mix, two market scenarios were compared. In the current environment (scenario 1), patients received current immunosuppressants agents (cyclosporine A, methotrexate, mycophenolate mofetil, and azathioprine) and dupilumab based on the current market share, and in the new environment (scenario 2), patients received upadacitinib (introduced to the formulary over 3 years) and all other immunosuppressants agents, as well as dupilumab, based on projected annual market shares.

Patients received treatments based on dosing per the prescribing information or recommended doses suggested by clinical trials, and incurred costs related to treatment acquisition, treatment administration, laboratory testing/procedure, and clinic visits. As the model calculations utilized annual cycles, it was assumed that patients receiving treatment would receive the same treatment for the entire year, and treatment discontinuation was not explicitly modelled. Costs related to treatment acquisition, treatment administration, laboratory testing/procedure, and clinic visits were calculated in each market scenario for each year of the time horizon.

The budget impact was calculated by comparing the total annual costs in scenario 2 with those in scenario 1. Results were reported in total annual, cumulative, per member per year (PMPY), per member per month (PMPM), and per treated member per month (PTMPM) costs. Model-building was done in accordance with guidelines and recommendations issued by the

International Society for Pharmacoeconomics and Outcomes Research (ISPOR).[68] No discounting was undertaken pursuant to these guidelines.[68] Figure 2 presents the budget impact model structure.

Figure 2. Budget Impact Model Structure [a]




[a] Model structure was developed in accordance with guidelines and recommendations issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).[68]

## 2.2 Population

The modelled patient population was the population indicated for upadacitinib (i.e., adult patients 18-65 years of age with moderate-to-severe AD whose disease is not adequately controlled with topical anti-inflammatory medications). The model only includes patients over 18 years of age because upadacitinib trials enrolled a relatively small number of patients under 18 and there is still uncertainty for using this treatment for adolescents.[58,60–62]

For model building, a one million covered lives were assumed. The number of patients eligible for treatment was calculated from the U.S. prevalence estimates for adults' patients with AD and moderate-to-severe AD.[16,69] Among all adult patients with moderate-to-severe AD, 5% were assumed to be treated with systemic immunosuppressant agents, and 13.4% with the biological therapy, dupilumab. Of the 5% of patients treated with immunosuppressant agents, it was assumed that 30.3%, 16.2%, 6.1%, and 47.5% were treated with cyclosporine A, mycophenolate mofetil, azathioprine, and methotrexate, respectively, based on a study that analyzed retrospective claims database.[66] According to the study, the remaining patients received systemic oral corticosteroids (73.4%) and phototherapy (8.2%).[66] Among patients treated with immunosuppressant agents and the biological therapy dupilumab, 0.68% were assumed to be new to treatment each year due to the incidence (1.7%) and the prevalence (40%) of moderate-to-severe AD among adults.[16,70] In all subsequent years of the model, the portion of upadacitinib patients new to treatment was consistent with the other modelled treatments (0.68%). The number of new patients with moderate-to-severe AD were assumed to be new to treatment each year of the time horizon and 66.50% of those would be covered by the private health insurance.[71] The prevalence of moderate-to-severe AD was assumed to remain constant. All-cause mortality for the modelled population was not considered. The treated population was therefore assumed to

remain constant over the modelled time horizon. Table 1 provides moderate-to-severe atopic dermatitis population estimates.

Table 1. Moderate-to-Severe Atopic Dermatitis Population Estimates

| Population characteristic | Base case % | Base case N |
|---|---|---|
| Patients living with moderate-to-severe atopic dermatitis | | |
| Total population (18-64 years) covered by private health insurance [a] | 100% | 1,000,000 |
| The prevalence of adults with atopic dermatitis [b] | 4.9% | 49,000 |
| With moderate-to-severe atopic dermatitis (eligible for upadacitinib) [c] | 40% | 19,600 |
| Eligible patients treated with immunosuppressant agents and dupilumab | 18.4% | 3,606 |
| Proportion treated with immunosuppressant agents [d, e] | 5% | 982 |
| Treated with cyclosporine A [f] | 30.3% | 297 |
| Treated with mycophenolate mofetil [f] | 16.2% | 159 |
| Treated with azathioprine [f] | 6.1% | 60 |
| Treated with methotrexate [f] | 47.5% | 466 |
| Proportion treated with biological therapy/dupilumab [d] | 13.4% | 2,626 |
| New immunosuppressant agents or biological therapy/dupilumab users | | |
| Proportion of new moderate-to-severe atopic dermatitis patients each year [g] | 0.68% | 25 |
| Proportion covered by private health insurance [h] | 0.45% | 16 |

[a] Hypothetical one million covered lives were assumed.
[b] Point prevalence of atopic dermatitis in adults in the United States was estimated at 4.9%.[69]
[c] It was assumed that 40% of atopic dermatitis patients have moderate-to-severe symptoms.[16]
[d] It was assumed that 5% and 13.4% of patients with moderate-to-severe atopic dermatitis received systemic immunosuppressants agents and dupilumab, respectively, based on a study that analyzed retrospective claims database.[66]
[e] Our estimates were based on a study that analyzed retrospective claims database that provided rounded decimal point proportions. Thus, there were an additional two immunosuppressant agent users.[66]
[f] It was assumed that 30.3%, 16.2%, 6.1%, 47.5% of patients using immunosuppressant agents received cyclosporine A, mycophenolate mofetil, azathioprine, and methotrexate, respectively, based on a study that analyzed retrospective claims database.[66]
[g] Based on a prospective cohort study; the incidence of atopic dermatitis was estimated at 1.7%. It was assumed that 0.68% of those had moderate-to-severe atopic dermatitis based on the previous prevalence estimates of 40%.[16,70]
[h] It was assumed that 66.5% of the new patients would be covered by the private health insurance, and of those, 0.45% would be the proportion of new patients each year and covered by the private health insurance.[71]

### 2.3 Market Shares

Current market shares before the introduction of upadacitinib (scenario 1) were based on different market estimates for each immunosuppressant agent and dupilumab. Market shares data for immunosuppressant agent are not publicly available. However, market shares for immunosuppressants agents were estimated based on a study that analyzed retrospective claims data on AD treatment patterns.[66] According to the study, methotrexate was the most common used immunosuppressant agent for the treatment of moderate-to-severe AD (47.5%), followed by cyclosporine A (30.3%), mycophenolate mofetil (16.2%), and azathioprine (6.1%). Therefore, methotrexate was assumed to hold a percentage share of 20% as it has been used as a first option agent among all immunosuppressant agents, cyclosporine A held a percentage share of 10% as a second option agent, and mycophenolate mofetil and azathioprine held a percentage share of 5% due to their limited data and clinical use in AD patients. Market share for dupilumab was estimated based on a published report regarding the exponential growth of biologic drugs for AD.[67] The report stated that biological treatments accounted for the highest market share of 42% in 2018 and continue to increase to a projected value of 77% in 2027.[67] The annual increase in market share between 2018 and 2027 is 3.8%.[67] From 2018 to 2022, a share of approximately 3.8% was added each year to calculate a share of 60% for dupilumab. Moreover, based on a study reporting the treatment pattern for AD patients, dupilumab (13.4%) has been used more than all the immunosuppressant agents (5%), and thus, higher market share compared to all immunosuppressant agents.[66] In scenario 2, a 2% annual market uptake for upadacitinib was assumed over 3 years. Upadacitinib market share was assumed to be taken proportionally from the other treatments so that the distribution of market shares across the other treatments remained the same as that in the current market. Annual market shares were multiplied by the total number

of patients treated each year to determine the number of patients receiving upadacitinib. Market shares were applied for the entire year, as patients did not switch or discontinue treatment during the year. Since market share data are not yet publicly available, the estimates used in this model may not reflect the actual market share of those treatments. Table 2 provides the market share estimates over the 3-year budget plan.

Table 2. Market Share Estimates Over the 3-year Budget Plan [a]

| Treatment | Current year | Year-1 | Year-2 | Year-3 |
|---|---|---|---|---|
| Cyclosporine A | 10% | 9.8% | 9.6% | 9.4% |
| Upadacitinib | 0% | 0.2% | 0.4% | 0.6% |
| Methotrexate | 20% | 19.6% | 19.2% | 18.8% |
| Upadacitinib | 0% | 0.4% | 0.8% | 1.2% |
| Mycophenolate mofetil | 5% | 4.9% | 4.8% | 4.7% |
| Upadacitinib | 0% | 0.1% | 0.2% | 0.3% |
| Azathioprine | 5% | 4.9% | 4.8% | 4.7% |
| Upadacitinib | 0% | 0.1% | 0.2% | 0.3% |
| Dupilumab | 60% | 58.8% | 57.6% | 56.4% |
| Upadacitinib | 0% | 1.2% | 2.4% | 3.6% |
| Market shares of immunosuppressant agents and dupilumab | 100% | 98% | 96% | 94% |
| Market share of upadacitinib | 0% | 2% | 4% | 6% |

[a] 2% annual uptake for upadacitinib was assumed over 3 years.

## 2.4 Costs

### 2.4.1 Drug Acquisition Costs

Costs were estimated from the private payer perspective and only considered direct medical and drug acquisition costs. Productivity loss costs and indirect costs were not considered.

Patients who received treatment incurred drug acquisition costs based on their dosing regimens per the prescribing information or the recommended doses suggested by clinical trials. The dosage regimen for immunosuppressant agents can differ considerably depending on many factors, including the severity of the patient's disease, patient's weight, and other medical

conditions that the patient may have.[39] For cyclosporine A, cost estimate has been made based on the most effective dosage regimen assessed in a body-weight–independent dosing clinical trial.[72] The dosage regimen for methotrexate was based on the most common dose used for adult patients with moderate-to-severe AD.[73] There is insufficient data regarding the optimal mycophenolate mofetil dose or the duration of therapy for adults with moderate-to-severe AD.[39] However, typical starting dose in dermatology of mycophenolate mofetil was used to for cost estimate.[74] The AAD has stated that the range of azathioprine is still unknown among patients with moderate-to-severe AD.[39] Although, we estimated the cost for azathioprine acquisition based on an average weight of ~ 70 kilograms (kg).[39]

Patients treated with dupilumab or upadacitinib incurred drug acquisition costs based on dosing regimens as described in the prescribing information.[75,76] For patients treated with dupilumab, additional drug acquisition costs were incurred for the treatment loading dose for newly diagnosed moderate-to-severe AD patients each year. For the remainder of the treated population, the drug acquisition costs were only incurred based on the maintenance dosing regimen. Table 3 provides the dosage regimen and the total annual costs per patient.

For cyclosporine A and mycophenolate mofetil, the annual acquisition costs were based on the average wholesale prices (AWPs) and discounted by 22% to estimate the wholesale acquisition costs (WACs).[77,78] All other treatments were based on the WACs for their annual costs.[79–82] Annual costs were calculated by multiplying the estimated annual treatment doses required by the treatment cost per dose. Co-pay and co-insurance were not considered. All costs were adjusted to 2022 U.S. dollars using the Consumer Price Index (CPI).[83] Table 4 provides the annual drug acquisition costs based on population estimates.

Table 3. Dosage Regimen and Annual Total Costs Per Patient

| Treatment | Dosage Form Unit Cost ($) | Units Per Year | AWP Per Patient Per Year ($) | WAC Per Patient Per Year ($) |
|---|---|---|---|---|
| Cyclosporine A[a]<br>Dose size 300 mg/day | 100 mg ($9.18)<br>25 mg ($2.30) | 730<br>1446 | $6,701<br>$3,358<br>= $10,059 | $5,227<br>$2,619<br>= $7,846 |
| Methotrexate [b]<br>Dose size 15 mg/week | 15 mg/0.4 ml ($706.22) | 12 | - | $8,475 |
| Mycophenolate mofetil [c]<br>Dose size 250 mg/twice daily | 250 mg ($9.26) | 730 | $6,760 | $5,273 |
| Azathioprine [d]<br>Dose size 150 mg/day | 100 mg ($9.19)<br>50 mg ($8.34) | 365<br>365 | - | $3,354<br>$3,044<br>= $6,398 |
| Dupilumab [e]<br>Dose size 300 mg/every two weeks | 300 mg/2 ml ($3,331.53) | 1 [f]<br>12 | - | $3,332<br>$39,978<br>= $43,310 |
| Upadacitinib [g]<br>Dose size 15 mg/day | 15 mg ($189.04) | 365 | - | $69,000 |

*WAC, wholesale acquisition cost; mg, milligram; ml, milliliter*

[a] Standard dose in adults with atopic dermatitis was estimated as 150-300 mg/day. The body-weight–independent dosing regimen of 300 mg/day was more effective than 150 mg/day.[72]

[b] Maintenance dose was estimated as 7.5-25 mg/week, and the most often dose used in adults was 15 mg/week.[73]

[c] Typical starting dose used in dermatology was estimated as 250 mg twice daily.[74]

[d] Cost was assumed based the dosage regimen of 150 mg per day (weight-based dosing assumes a ~ 70 kg patient as an average weight).[39]

[e] Recommended loading dose of 600 mg, followed by 300 mg given every other week.[75]

[f] Additional drug acquisition cost was incurred for the treatment loading dose for new patients each year.[75]

[g] Recommended dose was estimated as 15 mg daily for patients aged 18-64 years old.[76]

Table 4. Annual Drug Acquisition Costs Based on Population Estimates [a,b]

| Treatment | | Current year | Year-1 | Year-2 | Year-3 |
|---|---|---|---|---|---|
| | | Current environment (scenario 1) | | | |
| Cyclosporine A | Number of patients:<br>Costs: | 361<br>$2,830,470 | 355<br>$2,786,404 | 349<br>$2,741,882 | 344<br>$2,696,900 |
| Methotrexate | Number of patients:<br>Costs: | 721<br>$6,114,249 | 710<br>$6,019,060 | 699<br>$5,922,885 | 687<br>$5,825,717 |
| Mycophenolate mofetil | Number of patients:<br>Costs: | 180<br>$951,022 | 178<br>$936,216 | 175<br>$921,256 | 172<br>$906,143 |
| Azathioprine | Number of patients:<br>Costs: | 180<br>$1,154,082 | 178<br>$1,136,115 | 175<br>$1,117,961 | 172<br>$1,099,621 |
| Dupilumab [c] | Number of patients:<br>Costs: | 2164<br>$86,530,282 | 2131<br>$85,215,240 | 2097<br>$83,853,633 | 2062<br>$82,477,968 |
| | | New environment (scenario 2) | | | |
| Upadacitinib | Number of patients:<br>Costs: | 0<br>$0 | 72<br>$5,000,667 | 146<br>$10,046,560 | 219<br>$15,137,985 |

[a] Costs were based on the wholesale acquisition costs (WACs); co-pay and co-insurance were not included.
[b] All costs were adjusted to 2022 United States (U.S.) dollars using the Consumer Price Index (CPI).[83]
[c] Includes the number of patients new to treatment who received loading dose.

### 2.4.2 Other Costs

Based on the recommended dosing regimens for the applicable treatments, costs for administering treatments to patients were incurred. SC injections of methotrexate and dupilumab were administered at the clinic for the first visit by the physician and self-administered thereafter for new patients each year. All other treatments were administered orally and thus did not incur administration costs. The cost of SC injections was calculated based on the Physician Fee Schedule using Current Procedural Terminology (CPT) code.[84] The annual number of injections each year was multiplied by the associated unit cost per injection to calculate the annual costs of injection per patient.

For new treatment monitoring, all AD patients should be referred to a dermatologist after 3 months.[53] Additionally, treatment discontinuation was not explicitly modeled, so all patients

assumed to take the same treatment for the entire year. Thus, we assumed that all treated patients would need one clinic visits per year for disease and treatment monitoring (methotrexate and dupilumab required an additional clinic visit for the treatment administration by the physician). Costs per clinic visit were calculated based on the Physician Fee Schedule using CPT code for physician visits of intermediate complexity for 30-39 minutes.[84] The annual frequency of clinic visit was multiplied by the associated unit costs to calculate annual costs of clinic visits per patient.

In order to monitor the effects of treatments on the immune system, laboratory testing/procedure is required at the onset of treatment and periodically afterward. Consequently, all treated patients incurred costs for laboratory tests/procedure and patient monitoring on an annual basis. Annual laboratory testing/procedure resource use (i.e., creatinine levels, blood urea nitrogen, complete blood count, liver enzymes, serum lipids, magnesium, potassium, renal functions, hemoglobin, and chest x-ray) were based on estimated laboratory regimens or number of procedures in the prescribing information of each treatment. Costs per test or procedure were based on the Medicare Clinical Laboratory Fee Schedule (CLFS) using CPT codes.[84,85] Dupilumab does not require initial laboratory testing or ongoing lab monitoring, and thus, does not incur laboratory testing/procedure cost. The annual frequency of laboratory testing/procedure was multiplied by the associated unit costs to calculate annual costs of laboratory testing/procedure per patient.

All costs were adjusted to 2022 U.S. dollars using the CPI.[83] Table 5 provides the number of resource use and the total other costs per patient per year. Table 6 provides the annual other costs based on population estimates.

Table 5. Other Costs Per Patient Per Year

| Parameter | Cyclosporine A | Methotrexate | Mycophenolate mofetil | Azathioprine | Dupilumab | Upadacitinib |
|---|---|---|---|---|---|---|
| Laboratory tests [a] | | | | | | |
| *At the initiation of the treatment* | | | | | | |
| Creatinine levels | 1 | | | | | |
| BUN | 1 | | | | | |
| CBC | 1 | 1 | | | | 1 |
| Liver enzymes | 1 | 1 | | | | 1 |
| Serum lipids | 1 | | | | | 1 |
| Mg | 1 | | | | | |
| K | 1 | | | | | |
| Renal function | | 1 | | | | |
| Hemoglobin | | | | | | 1 |
| Chest x-ray | | 1 | | | | |
| *During the treatment* | | | | | | |
| Creatinine levels | 5 | | | | | |
| BUN | 5 | | | | | |
| CBC | 5 | 11 | 17 | 17 | | 3 |
| Serum lipids | | | | | | 3 |
| Liver enzymes | 5 | 5 | | | | 3 |
| Mg | 5 | | | | | |
| K | 5 | | | | | |
| Renal function | | 5 | | | | |
| Hemoglobin | | | | | | 3 |
| Total costs | $418 | $307 | $185 | $185 | $0.00 | $178 |
| Clinic visit and treatment administration | | | | | | |
| Number of visits | 1 | 2 | 1 | 1 | 2 | 1 |
| Unit cost per visit [b] | $152 | $152 | $152 | $152 | $152 | $152 |
| Unit cost per injection [c] | $0 | $18 | $0 | $0 | $18 | $0 |
| Total costs | $152 | $321 | $152 | $152 | $321 | $152 |
| Total other costs | $570 | $629 | $337 | $337 | $322 | $330 |

*BUN, blood urea nitrogen; CBC, complete blood count; Mg, magnesium; K, potassium*

[a] Costs indicated from the Medicare Clinical Laboratory Fee Schedule (CLFS). Costs were adjusted to 2022 United States (U.S.) dollars using the Consumer Price Index (CPI).[83–85]

[b] We assumed a one clinic visit per year. Costs were based on the Physician Fee Schedule using Current Procedural Terminology (CPT) code for physician visits for 30-39 minutes. The administration cost per treatment dose was based on the Physician Fee Schedule using CPT code for subcutaneous injection.[84]

[c] Methotrexate and dupilumab required treatment administration when starting the treatment. It was assumed a one additional visit for these two medications for treatment administration by the physician. Oral medications do not incur any drug administration costs; therefore, they incur only the costs of one visit.[84]

Table 6. Annual Other Costs Based on Population Estimates [a]

| Treatment | | Current year | Year-1 | Year-2 | Year-3 |
|---|---|---|---|---|---|
| | | Current environment (scenario 1) | | | |
| Cyclosporine A | Number of patients:<br>Costs: | 361<br>$180,427 | 355<br>$177,730 | 349<br>$174,890 | 344<br>$172,021 |
| Methotrexate | Number of patients:<br>Costs: | 721<br>$281,224 | 710<br>$277,613 | 699<br>$273,177 | 687<br>$268,695 |
| Mycophenolate mofetil | Number of patients:<br>Costs: | 180<br>$60,797 | 178<br>$59,850 | 175<br>$58,894 | 172<br>$57,928 |
| Azathioprine | Number of patients:<br>Costs: | 180<br>$60,797 | 178<br>$59,850 | 175<br>$58,894 | 172<br>$57,928 |
| Dupilumab | Number of patients:<br>Costs: | 2164<br>$329,231 | 2131<br>$325,740 | 2097<br>$320,535.22 | 2062<br>$315,276.66 |
| | | New environment (scenario 2) | | | |
| Upadacitinib | Number of patients:<br>Costs: | 0<br>$0 | 72<br>$20,690 | 146<br>$41,567 | 219<br>$62,632 |

[a] Costs were adjusted to 2022 United States (U.S.) dollars using the Consumer Price Index (CPI).[83]

### 2.5 Model Outcomes

The budget impact analysis estimated costs based on the calculated number of moderate-to-severe AD patients treated. Costs were calculated without discounting, as recommended by the ISPOR Task Force on Good Research Practices for budget impact models.[68] For each treatment, costs were organized by treatment acquisition costs and other costs. Other costs included resource use costs for drug administration, laboratory testing/procedure, and clinic visits. Costs were reported as annual total, cumulative, PMPM, PMPY, PTMPM costs. The incremental budget impact was calculated each year by comparing the total annual costs after the introduction of upadacitinib (year 1 through year 3) with the total annual costs for the current market without upadacitinib.

Two scenario analyses have been performed on the annual market uptake of upadacitinib (1% and 3%) versus (2% in the base case). Sensitivity analysis was performed to test the robustness of model outcomes and the uncertainty of model input data. A deterministic one-way sensitivity analysis was conducted by varying input values for AD prevalence, moderate-to-severe AD prevalence, and treatment acquisition costs of cyclosporine A, methotrexate, mycophenolate mofetil, azathioprine, dupilumab, and upadacitinib. Key parameters were varied from their default values using 95% confidence intervals (CI) ranges for parameters where data were leveraged from clinical trials (AD prevalence[69] and moderate-to-severe AD prevalence[16]) and ±50% for parameters with greater uncertainty (e.g., treatment acquisition costs) which was assumed to represent a reasonable range of uncertainty of dosage variation of these treatments. The effect of varying each input on the overall 3-year budget impact was measured, and the results were presented in a tornado diagram.

# CHAPTER 3. RESULTS

## 3.1 Base-Case Analysis

For one million covered lives, it was estimated that 3607 people would be treated for moderate-to-severe AD with immunosuppressant agents or dupilumab in the current year, and 16 people would be new to treatment in the first year and the following years, which they require additional loading dose, treatment administration, clinic visit, and initiation of treatment laboratory testing/procedure in their first year of treatment.

The total annual costs associated with immunosuppressant agents and dupilumab were $98.4 million for the current market without upadacitinib. Total annual costs after the introduction of upadacitinib were $102.0, $105.5, and $109.0 million in years 1 through 3,

respectively. Annual costs for upadacitinib ranged from $5.0 in year 1, $10.0 in year 2, and $15.2 million in year 3. The cumulative costs for upadacitinib were $30.3 million over 3 years, while overall cumulative costs across all treatments totaled approximately $316.6 million. Of the total costs, 99% was attributed to drug acquisition costs, while the remaining 1% of costs were attributed to other costs including treatment administration, laboratory testing/procedure, and clinic visits.

When comparing the market scenario with upadacitinib and the market scenario without upadacitinib, introducing upadacitinib increased the total cost by $3.5, $7.0, and $10.5 million in years 1 through 3, respectively, resulting in a cumulative increase of $21.1 million in years 1 through 3. The incremental PMPY costs were $3.52, $7.04, and $10.59 in years 1–3, respectively, resulting in an increased PMPM costs of $0.29 in year 1, $0.59 in year 2, and $0.88 in year 3. The incremental PTMPM costs were $70.77, $140.72, and $210.67 in years 1–3, respectively. The average cumulative budget impact was $7.05 PMPY, $0.59 PMPM, and $140.72 PTMPM. Table 7 provides the base-case analysis results of the budget impact model.

Table 7. Base-Case Results

| | Current year | Year-1 | Year-2 | Year-3 | Cumulative [a] |
|---|---|---|---|---|---|
| Total number of patients receiving treatment | 3607 | | | | |
| Number new to treatment | 0 | 16 | 16 | 16 | 49 |
| Total New number of patients receiving treatment each year | 3607 | 3624 | 3640 | 3657 | 10920 |
| Total annual costs [b] ($) | $98,492,581 | $102,015,174 | $105,532,133 | $109,078,814 | $316,626,122 |
| Cyclosporine A | $3,010,897 | $2,964,134 | $2,916,771 | $2,868,920 | $8,749,825 |
| Drug costs | $2,830,470 | $2,786,404 | $2,741,882 | $2,696,900 | $8,225,185 |
| Other costs [c] | $180,427 | $177,730 | $174,890 | $172,021 | $524,640 |
| Methotrexate | $6,395,473 | $6,296,673 | $6,196,062 | $6,094,412 | $18,587,146 |
| Drug costs | $6,114,249 | $6,019,060 | $5,922,885 | $5,825,717 | $17,767,662 |
| Other costs [c] | $281,224 | $277,613 | $273,177 | $268,695 | $819,485 |
| Mycophenolate mofetil | $1,011,819 | $996,066 | $980,150 | $964,071 | $2,940,287 |
| Drug costs | $951,022 | $936,216 | $921,256 | $906,143 | $2,763,615 |
| Other costs [c] | $60,797 | $59,850 | $58,894 | $57,928 | $176,673 |
| Azathioprine | $1,214,879 | $1,195,965 | $1,176,856 | $1,157,549 | $3,530,369 |
| Drug costs | $1,154,082 | $1,136,115 | $1,117,961 | $1,099,621 | $3,353,697 |
| Other costs [c] | $60,797 | $59,850 | $58,894 | $57,928 | $176,673 |
| Dupilumab | $86,859,513 | $85,540,980 | $84,174,168 | $82,793,245 | $252,508,393 |
| Drug costs | $86,530,282 | $85,215,240 | $83,853,633 | $82,477,968 | $251,546,841 |
| Other costs [c] | $329,231 | $325,740 | $320,535 | $315,277 | $961,552 |
| Upadacitinib | - | $5,021,357 | $10,088,126 | $15,200,617 | $30,310,101 |
| Drug costs | - | $5,000,667 | $10,046,560 | $15,137,985 | $30,185,211 |
| Other costs [c] | - | $20,690 | $41,567 | $62,632 | $124,889 |
| Incremental budget impact versus current market ($) | | | | | |
| Total costs | - | $3,522,594 | $7,039,553 | $10,586,233 | $21,148,379 |
| Total PMPY costs [d] | - | $3.52 | $7.04 | $10.59 | $7.05 |
| Total PMPM costs [d] | - | $0.29 | $0.59 | $0.88 | $0.59 |
| Total PTMPM costs [d] | - | $70.77 | $140.72 | $210.67 | $140.72 |

*PMPM, per member per month; PMPY, per member per year; PTMPM, per treated member per month*

[a] Cumulative result are the sum of results from year 1 to year 3.

[b] Total annual costs include drug acquisition costs, treatment administration, laboratory testing/procedure, and clinic visits.

[c] Other costs include treatment administration, laboratory testing/procedure, and clinic visits.

[d] PMPY, PMPM, and PTMPM costs are based on a one million covered lives. 'Treated members' includes all patients with moderate-to-severe atopic dermatitis treated with immunosuppressant agents or dupilumab for each year. The costs listed in the 'Cumulative' column are the average PMPY, PMPM, and PTMPM costs over the 3-year time horizon.

### 3.2 Scenario Analysis

Using a 1% annual uptake for upadacitinib (versus 2% in the base case) resulted in a reduction of the total costs to $2.0 $3.9, and $5.9 million (versus $3.5, $7.0, and $10.5 million in the base case) in years 1–3, respectively. The cumulative total cost from adding upadacitinib to the formulary decreased to $11.9 million (versus $21.1 million in the base case), and the cumulative PMPY, PMPM, and PTMPM cost decreased to $3.99, $0.33, $70.77 (versus $7.04, $0.59, and $140.72 in the base case) in years 1–3, respectively.

Using a 3% annual uptake for upadacitinib (versus 2% in the base case) resulted in an increase of the total costs to $5.0, $10.0, and $15.1 million (versus $3.5, $7.0, and $10.5 million in the base case) in years 1–3, respectively. The cumulative total cost from adding upadacitinib to the formulary increased to $30.3 million (versus $21.1 million in the base case), and the cumulative PMPY, PMPM, and PTMPM cost increased to $10.11, $0.84, and $210.67 (versus $7.04, $0.59, and $140.72 in the base case) in years 1–3, respectively.

A 3% annual market uptake of upadacitinib resulted in higher impact on the private payer budget compared to 1% and 2% annual market uptake. The 1% market uptake of upadacitinib resulted in a less budget impact for private payers compared to 2% annual market uptake. However, both market uptake scenarios resulted in an impact on the private payer budget with no saving. Table 8 provides the scenario analyses results.

Table 8. Scenario Analyses Results

| Uptake | | Incremental costs | | | |
|---|---|---|---|---|---|
| | | Total costs | PMPY [d] | PMPM [d] | PTMPM [d] |
| Base case (Annual uptake of 2%) | Year-1 | $3,522,594 | $3.52 | $0.29 | $70.77 |
| | Year-2 | $7,039,553 | $7.04 | $0.59 | $140.72 |
| | Year-3 | $10,586,233 | $10.59 | $0.88 | $210.67 |
| | Cumulative [a] | $21,148,379 | $7.04 | $0.59 | $140.72 |
| Scenario 1 (Annual uptake of 1%) | Year-1 | $2,001,648 | $2.00 | $0.17 | $35.79 |
| | Year-2 | $3,983,906 | $3.98 | $0.33 | $70.77 |
| | Year-3 | $5,982,037 | $5.98 | $0.50 | $105.74 |
| | Cumulative [a] | $11,967,592 | $3.99 | $0.33 | $70.77 |
| Scenario 2 (Annual uptake of 3%) | Year-1 | $5,043,539 | $5.04 | $0.42 | $105.74 |
| | Year-2 | $10,095,199 | $10.10 | $0.84 | $210.67 |
| | Year-3 | $15,190,429 | $15.19 | $1.27 | $315.60 |
| | Cumulative [a] | $30,329,167 | $10.11 | $0.84 | $210.67 |

*PMPM, per member per month; PMPY, per member per year; PTMPM, per treated member per month*

[a] Cumulative result are the sum of results from year 1 to year 3.

[d] PMPY, PMPM, and PTMPM costs were based on a one million covered lives. 'Treated members' includes all patients with moderate-to-severe atopic dermatitis treated with immunosuppressant agents or dupilumab for each year. The costs listed in the 'Cumulative' column are the average PMPY, PMPM, and PTMPM costs over the 3-year time horizon.

### 3.3 Sensitivity Analysis

Sensitivity analysis results were most sensitive to the treatment acquisition costs for upadacitinib, followed by moderate-to-severe AD prevalence. AD prevalence and the acquisition costs for dupilumab had a minimal impact. The acquisition costs for cyclosporine A, methotrexate, mycophenolate mofetil, and azathioprine, had no impact on the incremental budget. Nevertheless, even the reduction of 50% of the acquisition cost of upadacitinib would still result in an impact on the private payer's budget. Table 9 provides sensitivity analysis

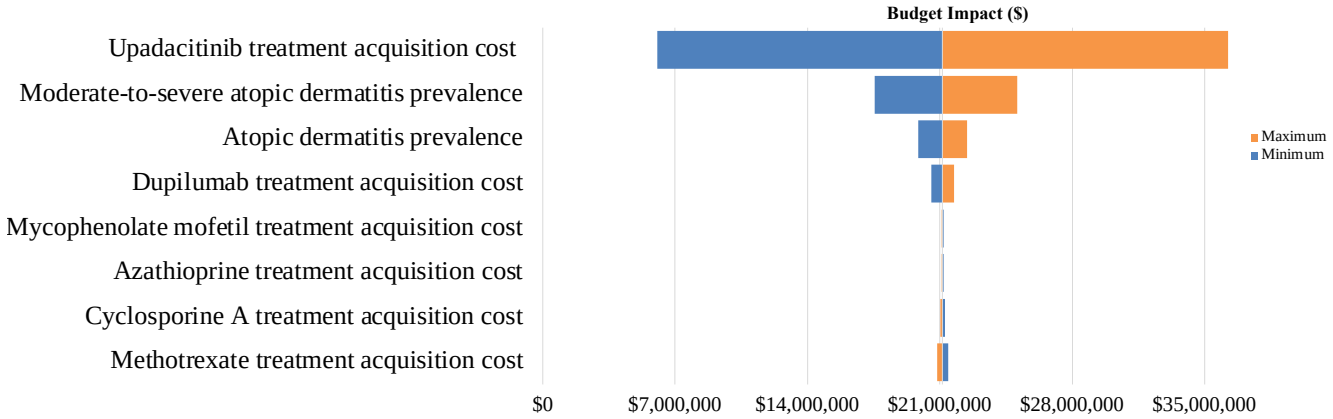
incremental cumulative total costs results. Figure 3 presents the impacts of key model parameters on the total annual costs over 3 years.

Table 9. Sensitivity Analysis Incremental Cumulative Total Costs Results

| Parameter | Using Minimum value | Using Maximum value |
|---|---|---|
| Methotrexate treatment acquisition cost [a] | $21,435,911 | $20,860,800 |
| Cyclosporine A treatment acquisition cost [a] | $21,281,492 | $21,015,267 |
| Azathioprine treatment acquisition cost [a] | $21,202,654 | $21,094,105 |
| Mycophenolate mofetil treatment acquisition cost [a] | $21,193,105 | $21,103,655 |
| Dupilumab treatment acquisition cost [a] | $20,532,470 | $21,764,295 |
| Atopic dermatitis prevalence [b] | $19,853,581 | $22,443,178 |
| Moderate-to-severe atopic dermatitis prevalence [c] | $17,537,684 | $25,086,375 |
| Upadacitinib treatment acquisition cost [a] | $6,055,774 | $36,240,985 |

[a] ±50% variation of drug acquisition costs.
[b] 95% confidence interval (CI): 4.6% - 5.2%.[69]
[c] 95% confidence interval (CI): 33.90% - 46.40%.[16]

Figure 3. Sensitivity Analysis Tornado Diagram [a]




[a] One-way deterministic sensitivity analysis: impact of changes of input values on the cumulative budget impact over 3 years.
Note: drug acquisition costs were varied uniformly by ± 50% of the base-case values, while 95% confidence intervals (CI) ranges were used for atopic dermatitis prevalence and moderate-to-severe atopic dermatitis prevalence.

# CHAPTER 4. DISCUSSION AND LIMITATIONS

## 4.1 Discussion

A budget impact analysis was conducted to estimate the impact of introducing and increasing the market share of upadacitinib to a private payer's budget over 3 years. To our knowledge, no prior analysis has assessed the potential budget impact of upadacitinib for the treatment of uncontrolled moderate-to-severe AD in the U.S. The result of the analysis showed that, for the assumed market uptake and market shares of other treatments, the introduction of upadacitinib had a high impact on a private payer's budget. Total costs were almost completely attributed to drug acquisition costs rather than other costs related to treatment administration, laboratory testing/procedure, and clinic visits. Compared with a market scenario without upadacitinib, the total costs would increase from the first year forward after introducing upadacitinib to the market for the treatment of uncontrolled moderate-to-severe AD. Incremental PMPY, PMPM, and PTMPM costs increase cumulatively by $7.05, $0.59, and $140.72 over 3 years, respectively. The results were largely driven by the differences in drug acquisition costs between upadacitinib and the other treatments.

As a result of the low market uptake of upadacitinib and the high market share of immunosuppressant agents and dupilumab, there was a smaller increase in total cost in the first year of upadacitinib introduction compared with subsequent years. After the first year, there was an increase in the annual market uptake of upadacitinib and decrease in the market share of the other treatments. As of that, the total costs after introduction of upadacitinib increased due to the increase of number of patients taking the new treatment in the following years.

When comparing upadacitinib with immunosuppressant agents, the drug acquisition cost per patient per year in maintenance treatment of upadacitinib ($69,000) is considerably higher

than the drug acquisition cost of cyclosporine A ($7,846), methotrexate ($8,475), mycophenolate mofetil ($5,273), and azathioprine ($6,398). Both upadacitinib and immunosuppressant agents incurred other costs related to laboratory testing/procedure, treatment administration, and clinic visit. Cyclosporine A required more initial and ongoing laboratory tests and procedure which resulted in higher total other costs ($570) compared to upadacitinib ($330). Methotrexate required additional clinic visit and incur additional cost for the treatment administration, which also resulted in higher other costs ($629) compared to upadacitinib ($330). Mycophenolate mofetil ($337) and azathioprine ($337) incur similar other costs compared to upadacitinib ($330). However, the high acquisition cost of upadacitinib compensated for the higher other costs of cyclosporine A and methotrexate, and thus, resulted in higher total costs when compared to all immunosuppressant agents. Furthermore, dupilumab's drug acquisition costs ($43,310) were higher than all immunosuppressant agents. When comparing dupilumab with upadacitinib, dupilumab incur lower acquisition cost per patient per year ($43,310) than upadacitinib ($69,000), but the difference in drug acquisition costs between dupilumab and upadacitinib was lower than all immunosuppressant agents and upadacitinib. Additionally, dupilumab does not require initial or ongoing laboratory monitoring, and incur only the additional clinic visit and treatment administration costs. The resulted total other cost of dupilumab ($322) was similar to upadacitinib ($330) which incurred initiation and ongoing laboratory tests and clinic visit costs. Although dupilumab has a higher acquisition cost compared to all immunosuppressant agents, a lower acquisition cost difference from upadacitinib, and a higher market share of dupilumab among upadacitinib and immunosuppressant agents, the incremental total costs still increased when the number of annual upadacitinib users increased. This increase contributed to the

increase in the total, PMPY, PMPM, and PTMPM costs during the subsequent years of upadacitinib introduction.

Scenario analysis demonstrated that higher uptake of upadacitinib may further increase total costs for moderate-to-severe AD, especially when market share is taken from drugs with less expensive annual acquisition costs for maintenance treatment, such as methotrexate, cyclosporine A, mycophenolate mofetil, and azathioprine. Both market uptake scenarios resulted in an impact on the private payer budget. Sensitivity analysis demonstrated that the overall costs were almost attributed to the acquisition cost of upadacitinib, followed by moderate-to-severe AD prevalence. AD prevalence and the acquisition costs for dupilumab had a minimal impact. There would still be an impact in the budget of private payers even if the acquisition cost of upadacitinib was cut in half (with no saving).

While previous studies have examined the budget impact for various AD treatments, no studies have included systemic immunosuppressant agents, dupilumab, or upadacitinib among the treatment options for uncontrolled moderate-to-severe AD.[86–88] An ICER report discussed a budget impact analysis results of several new treatment options, including upadacitinib, and the replacement of these options with dupilumab plus usual care (10% mix) or usual care alone (90%) over five years. Each year, they assigned 103,200 new individuals to the new treatments. For all prices evaluated, their analysis showed that the percentage of patients that could be treated by the new treatments within that pre-specified budget threshold was between 8% and 79% for all prices evaluated.[65] No further information was published regarding their analysis.

### 4.2 Limitations

The prevalence of AD and moderate-to-severe AD were assumed to remain constant over the modelled time horizon. Recent data showed that the prevalence of AD is still increasing.[89–91]

However, researchers stated that the definitions and measurements of AD have been problematic, leading to difficulties in differentiating real changes in disease prevalence from secular changes in diagnosis.[89–91] At this point, the evidence does not support a conclusion that AD or moderate-to-severe AD is increasing over time. In addition, our sensitivity analysis demonstrated that changes in prevalence rates of AD had a minimal impact on the private payer budget. In other words, the increase in the prevalence of AD would still result in an impact on the budget of private payers. Furthermore, the findings from our analysis indicated that the budget impact was largely driven by the acquisition costs associated with upadacitinib.

The age of patients with moderate-to-severe AD was not stratified in our model. Age stratification could affect the drug dose, the number of laboratory tests, and thus, the cost incurred for each patient. Epidemiological data for our estimates indicated however, that there is no considerable difference in the prevalence between young and old adults, and prevalence differs significantly only between children and adults.[16,69]

Considering that drug acquisition costs were based on recent WACs, individual costs may differ depending on other treatments not considered in this analysis, such as biosimilars and topical anti-inflammatory medications for acute flare treatment. Manufacturer discounts and rebates can also affect drug acquisition costs. We were unable to consider discounts or rebates since actual amounts can vary from market to market and are generally proprietary information.

A Medicare reimbursement rate was used to estimate the costs of laboratory testing/procedure, treatment administration, and clinic visits. Since not all health care providers are reimbursed at the same rate, and private health insurances incur higher reimbursement rates than Medicare and Medicaid[92], we chose to use the Medicare reimbursement rate because, first, private payer reimbursement rates are negotiated privately with different providers and are

therefore not publicly available. Second, the Medicare reimbursement rate is higher than Medicaid reimbursement rate.[93] Accordingly, laboratory testing/procedure, treatment administration, and clinic visits were estimated using the highest reimbursement rate that is publicly available. Our result, however, could underestimate costs incurred for laboratory testing/procedure, treatment administration, and clinic visits.

Market shares and market landscapes may change over time in the real world as new treatments may enter the market.[47,54] Because there are no biosimilars marketed in the U.S. for any of the treatments included in this analysis, we did not include biosimilars in our analysis. However, the introduction of biosimilars could affect our current market share estimations.

As all immunosuppressant agents and upadacitinib have similar serious adverse event profiles, and laboratory tests, the cost of treating serious adverse events was not taken into account in our analysis.

This budget impact analysis did not consider treatment response and assumed 100% adherence to therapy for each year of the modeled time horizon. If a more effective treatment results in a decrease in health care resource use, such differences may impact costs. The use of topical anti-inflammatory medications for acute flares management could affect the treatment response and, therefore, adherence for those patients.[94] However, patient adherence to treatments is largely based on how many flares the patient may experience.[94,95] Anti-inflammatory medications that the patient can buy over the counter (OTC) or basic management that the patient should follow can affect the management of the disease and treatment response, and thus, the adherence.

## CHAPTER 5. CONCLUSION

For the assumed market uptake and market shares, the introduction of upadacitinib had a high impact on the U.S. private payer's budget. The introduction of upadacitinib, with a 2% annual uptake over 3 years, is expected to have a financial impact to the U.S. private payer budget and thus, it may increase the cost of treating patients with moderate-to-severe AD whose disease is not adequately controlled with topical anti-inflammatory medications. Although the results of the scenarios were consistent, the future uptake of biosimilars and treatment adherence may affect the overall total costs associated with treating uncontrolled moderate-to-severe AD patients.

This study is the first step in addressing the impact of upadacitinib on the U.S. private payer's budget. Due to upadacitinib's impact on private payer budgets, it may make it harder for American patients to access newer treatments for moderate-to-severe AD. However, because of the high cost of upadacitinib that resulted in an impact on the private payer's budget, questions may remain about the value of this new therapy. Further studies are needed to provide a more real-world data to assess the impact of changes in essential drugs for moderate-to-severe AD patients whose disease is not adequately controlled with topical anti-inflammatory medications in the U.S.

# APPENDIX A
# SUPPLEMENTAL INFORMATION OF CHAPTER 2

## A.1 Treatment Mix (market shares and market uptake):

| Parameter | Current year | Year-1 | Year-2 | Year-3 |
|---|---|---|---|---|
| Number of patients with moderate-to-severe atopic dermatitis treated with immunosuppressant agents or dupilumab each year | 3607 | 3624 | 3640 | 3657 |
| Patients with moderate-to-severe atopic dermatitis treated with systemic immunosuppressant agents | | | | |
| Cyclosporine A | 10.0% | 9.8% | 9.6% | 9.4% |
| Upadacitinib | 0.0% | 0.2% | 0.4% | 0.6% |
| Number of new patients who receive cyclosporine A | 0 | 2 | 2 | 2 |
| Number of patients who receive cyclosporine A | 361 | 355 | 349 | 344 |
| Number of patients who receive upadacitinib | 0 | 7 | 15 | 22 |
| Methotrexate | 20.0% | 19.6% | 19.2% | 18.8% |
| Upadacitinib | 0.0% | 0.4% | 0.8% | 1.2% |
| Number of new patients who receive methotrexate | 0 | 3 | 3 | 3 |
| Number of patients who receive methotrexate | 721 | 710 | 699 | 687 |
| Number of patients who receive upadacitinib | 0 | 14 | 29 | 44 |
| Mycophenolate mofetil | 5.0% | 4.9% | 4.8% | 4.7% |
| Upadacitinib | 0.0% | 0.1% | 0.2% | 0.3% |
| Number of new patients who receive mycophenolate mofetil | 0 | 1 | 1 | 1 |
| Number of patients who receive mycophenolate mofetil | 180 | 178 | 175 | 172 |
| Number of patients who receive upadacitinib | 0 | 4 | 7 | 11 |
| Azathioprine | 5.0% | 4.9% | 4.8% | 4.7% |
| Upadacitinib | 0.0% | 0.1% | 0.2% | 0.3% |
| Number of new patients who receive azathioprine | 0 | 1 | 1 | 1 |
| Number of patients who receive azathioprine | 180 | 178 | 175 | 172 |
| Number of patients who receive upadacitinib | 0 | 4 | 7 | 11 |
| Patients with moderate-to-severe atopic dermatitis treated with dupilumab | | | | |
| Dupilumab | 60.0% | 58.8% | 57.6% | 56.4% |
| Upadacitinib | 0.0% | 1.2% | 2.4% | 3.6% |
| Number of new patients who receive dupilumab | 0 | 10 | 9 | 9 |
| Number of patients who receive dupilumab | 2164 | 2131 | 2097 | 2062 |
| Number of patients who receive upadacitinib | 0 | 43 | 87 | 132 |
| Total market shares of current treatments and annual uptake of upadacitinib | | | | |
| Market shares of immunosuppressant agents and dupilumab | 100% | 98% | 96% | 94% |
| Market share of updacitinib | 0.0% | 2.0% | 4.0% | 6.0% |
| Total number of patients who may receive all treatments (except upadacitinib) each year | 3607 | 3551 | 3494 | 3437 |
| Number of new patients who receive upadacitinib | 0 | 0 | 1 | 1 |
| Total number of patients who may receive upadacitinib each year based on market share | 0 | 72 | 146 | 219 |

## A.2 Estimated Other Costs (laboratory test/procedure costs):

| Treatments/laboratory tests or procedure (CPT code) | Number of tests per year | Unit cost per tests ($) | Total costs per patient per year ($) |
|---|---|---|---|
| Cyclosporine A | | | |
| At the initiation of the treatment | | | |
| Creatinine levels (CPT:82565) | 1 | $7.18 | $7.18 |
| BUN (CPT:84520) | 1 | $5.54 | $5.54 |
| CBC (CPT:85025) | 1 | $10.88 | $10.88 |
| Liver enzymes (CPT:80076) | 1 | $11.44 | $11.44 |
| Serum lipids (CPT:80061) | 1 | $18.75 | $18.75 |
| Magnesium (CPT:83735) | 1 | $9.38 | $9.38 |
| Potassium (CPT:84132) | 1 | $6.44 | $6.44 |
| During the treatment | | | |
| Creatinine levels (CPT:82565) | 5 | $7.18 | $35.90 |
| BUN (CPT:84520) | 5 | $5.54 | $27.70 |
| CBC (CPT:85025) | 5 | $10.88 | $54.40 |
| Liver enzymes (CPT:80076) | 5 | $11.44 | $57.20 |
| Serum lipids (CPT:80061) | 5 | $18.75 | $93.75 |
| Magnesium (CPT:83735) | 5 | $9.38 | $46.90 |
| Potassium (CPT:84132) | 5 | $6.44 | $32.20 |
| | | | $417.66 |
| Methotrexate | | | |
| At the initiation of the treatment | | | |
| CBC (CPT:85025) | 1 | $10.88 | $10.88 |
| Liver enzymes (CPT:80076) | 1 | $11.44 | $11.44 |
| Renal function tests (CPT:80069) | 1 | $12.16 | $12.16 |
| Chest x-ray (CPT:71046) | 1 | $34.61 | $34.61 |
| During the treatment | | | |
| CBC (CPT:85025) | 11 | $10.88 | $119.68 |
| Liver enzymes (CPT:80076) | 5 | $11.44 | $57.20 |
| Renal function tests (CPT:80069) | 5 | $12.16 | $60.80 |
| | | | $306.77 |
| Mycophenolate mofetil | | | |
| At the initiation of the treatment | | | |
| No lab tests | 0 | $0.00 | $0.00 |

| | | | |
|---|---|---|---|
| During the treatment | | | |
| CBC (CPT:85025) | 17 | $10.88 | $184.96 |
| | | | $184.96 |
| Azathioprine | | | |
| At the initiation of the treatment | | | |
| No lab tests | 0 | $0.00 | $0.00 |
| During the treatment | | | |
| CBC (CPT:85025) | 17 | $10.88 | $184.96 |
| | | | $184.96 |
| Dupilumab | | | |
| At the initiation of the treatment | | | |
| No lab tests | 0 | $0.00 | $0.00 |
| During the treatment | | | |
| No lab tests | 0 | $0.00 | $0.00 |
| | | | $0.00 |
| Upadacitinib | | | |
| At the initiation of the treatment | | | |
| Hemoglobin (CPT:85018) | 1 | $3.32 | $3.32 |
| CBC (CPT:85025) | 1 | $10.88 | $10.88 |
| Serum lipids (CPT:80061) | 1 | $18.75 | $18.75 |
| Liver enzymes (CPT:80076) | 1 | $11.44 | $11.44 |
| During the treatment | | | |
| Hemoglobin (CPT:85018) | 3 | $3.32 | $9.96 |
| CBC (CPT:85025) | 3 | $10.88 | $32.64 |
| Serum lipids (CPT:80061) | 3 | $18.75 | $56.25 |
| Liver enzymes (CPT:80076) | 3 | $11.44 | $34.32 |
| | | | $177.56 |

## A.3 Estimated Other Costs (physician visits and treatment administration costs):

| Treatments (CPT code) | Number of visits per year | Unit cost per visit ($) | Number of injections per year | Unit cost per injection ($) | Total number of visits per patient per year | Total costs per patient per year ($) |
|---|---|---|---|---|---|---|
| Cyclosporine A (CPT:99214) | 1 | $152.11 | 0 | $0.00 | 1 | $152.11 |
| Methotrexate (CPT:99214) (CPT: 96372) | 1 | $152.11 | 1 | $17.53 | 2 | $321.75 |
| Mycophenolate mofetil (CPT:99214) | 1 | $152.11 | 0 | $0.00 | 1 | $152.11 |
| Azathioprine (CPT:99214) | 1 | $152.11 | 0 | $0.00 | 1 | $152.11 |
| Dupilumab (CPT:99214) (CPT: 96372) | 1 | $152.11 | 1 | $17.53 | 2 | $321.75 |
| Upadacitinib (CPT:99214) | 1 | $152.11 | 0 | $0.00 | 1 | $152.11 |

## APPENDIX B
## SUPPLEMENTAL INFORMATION OF CHAPTER 3

### B.1 Budget Impact: Annual Costs:

| Cost outcomes | Current year | Year-1 | Year-2 | Year-3 |
|---|---|---|---|---|
| Cyclosporine A | | | | |
| Drug costs | $2,830,470.11 | $2,786,404.11 | $2,741,881.69 | $2,696,899.64 |
| Other costs | $180,426.72 | $177,729.54 | $174,889.70 | $172,020.54 |
| Total cyclosporine A costs | $3,010,896.83 | $2,964,133.65 | $2,916,771.39 | $2,868,920.18 |
| Methotrexate | | | | |
| Drug costs | $6,114,249.37 | $6,019,060.04 | $5,922,884.80 | $5,825,716.67 |
| Other costs | $281,224.13 | $277,612.64 | $273,176.82 | $268,695.21 |
| Total methotrexate costs | $6,395,473.50 | $6,296,672.69 | $6,196,061.62 | $6,094,411.88 |
| Mycophenolate mofetil | | | | |
| Drug costs | $951,021.53 | $936,215.60 | $921,256.33 | $906,142.62 |
| Other costs | $60,796.98 | $59,850.46 | $58,894.15 | $57,927.96 |
| Total mycophenolate mofetil costs | $1,011,818.50 | $996,066.07 | $980,150.48 | $964,070.58 |
| Azathioprine | | | | |
| Drug costs | $1,154,082.03 | $1,136,114.77 | $1,117,961.42 | $1,099,620.66 |
| Other costs | $60,796.98 | $59,850.46 | $58,894.15 | $57,927.96 |
| Total azathioprine costs | $1,214,879.01 | $1,195,965.24 | $1,176,855.57 | $1,157,548.61 |
| Dupilumab | | | | |
| Drug costs | $86,530,281.78 | $85,215,240.12 | $83,853,632.76 | $82,477,968.49 |
| Other costs | $329,231.14 | $325,740.04 | $320,535.22 | $315,276.66 |
| Total dupilumab costs | $86,859,512.92 | $85,540,980.16 | $84,174,167.97 | $82,793,245.16 |
| Upadacitinib | | | | |
| Drug costs | $0.00 | $5,000,666.76 | $10,046,559.55 | $15,137,985.14 |
| Other costs | $0.00 | $20,689.89 | $41,566.90 | $62,632.29 |
| Total upadacitinib costs | $0.00 | $5,021,356.65 | $10,088,126.45 | $15,200,617.43 |
| Total annual costs | $98,492,580.76 | $102,015,174.45 | $105,532,133.48 | $109,078,813.83 |
| Incremental budget impact versus current market | | | | |
| Total costs | - | $3,522,593.69 | $7,039,552.72 | $10,586,233.07 |

## B.2 Budget Impact: Per Member Per Year (PMPY):

| Cost outcomes | Current year | Year-1 | Year-2 | Year-3 |
|---|---|---|---|---|
| Cyclosporine A | | | | |
| Drug costs | $2.83 | $2.79 | $2.74 | $2.70 |
| Other costs | $0.18 | $0.18 | $0.17 | $0.17 |
| Total cyclosporine A costs | $3.01 | $2.96 | $2.92 | $2.87 |
| Methotrexate | | | | |
| Drug costs | $6.11 | $6.02 | $5.92 | $5.83 |
| Other costs | $0.28 | $0.28 | $0.27 | $0.27 |
| Total methotrexate costs | $6.40 | $6.30 | $6.20 | $6.09 |
| Mycophenolate mofetil | | | | |
| Drug costs | $0.95 | $0.94 | $0.92 | $0.91 |
| Other costs | $0.06 | $0.06 | $0.06 | $0.06 |
| Total mycophenolate mofetil costs | $1.01 | $1.00 | $0.98 | $0.96 |
| Azathioprine | | | | |
| Drug costs | $1.15 | $1.14 | $1.12 | $1.10 |
| Other costs | $0.06 | $0.06 | $0.06 | $0.06 |
| Total azathioprine costs | $1.21 | $1.20 | $1.18 | $1.16 |
| Dupilumab | | | | |
| Drug costs | $86.53 | $85.22 | $83.85 | $82.48 |
| Other costs | $0.33 | $0.33 | $0.32 | $0.32 |
| Total dupilumab costs | $86.86 | $85.54 | $84.17 | $82.79 |
| Upadacitinib | | | | |
| Drug costs | $0.00 | $5.00 | $10.05 | $15.14 |
| Other costs | $0.00 | $0.02 | $0.04 | $0.06 |
| Total upadacitinib costs | $0.00 | $5.02 | $10.09 | $15.20 |
| Total PMPY costs | $98.49 | $102.02 | $105.53 | $109.08 |
| Incremental budget impact versus current market | | | | |
| Total PMPY costs | - | $3.52 | $7.04 | $10.59 |

## B.3 Budget Impact: Per Member Per Month (PMPM):

| Cost outcomes | Current year | Year-1 | Year-2 | Year-3 |
|---|---|---|---|---|
| Cyclosporine A | | | | |
| Drug costs | $0.24 | $0.23 | $0.23 | $0.22 |
| Other costs | $0.02 | $0.01 | $0.01 | $0.01 |
| Total cyclosporine A costs | $0.25 | $0.25 | $0.24 | $0.24 |
| Methotrexate | | | | |
| Drug costs | $0.51 | $0.50 | $0.49 | $0.49 |
| Other costs | $0.02 | $0.02 | $0.02 | $0.02 |
| Total methotrexate costs | $0.53 | $0.52 | $0.52 | $0.51 |
| Mycophenolate mofetil | | | | |
| Drug costs | $0.08 | $0.08 | $0.08 | $0.08 |
| Other costs | $0.01 | $0.00 | $0.00 | $0.00 |
| Total mycophenolate mofetil costs | $0.08 | $0.08 | $0.08 | $0.08 |
| Azathioprine | | | | |
| Drug costs | $0.10 | $0.09 | $0.09 | $0.09 |
| Other costs | $0.01 | $0.00 | $0.00 | $0.00 |
| Total azathioprine costs | $0.10 | $0.10 | $0.10 | $0.10 |
| Dupilumab | | | | |
| Drug costs | $7.21 | $7.10 | $6.99 | $6.87 |
| Other costs | $0.03 | $0.03 | $0.03 | $0.03 |
| Total dupilumab costs | $7.24 | $7.13 | $7.01 | $6.90 |
| Upadacitinib | | | | |
| Drug costs | $0.00 | $0.42 | $0.84 | $1.26 |
| Other costs | $0.00 | $0.00 | $0.00 | $0.01 |
| Total upadacitinib costs | $0.00 | $0.42 | $0.84 | $1.27 |
| Total PMPM costs | $8.21 | $8.50 | $8.79 | $9.09 |
| Incremental budget impact versus current market | | | | |
| Total PMPM costs | - | $0.29 | $0.59 | $0.88 |

## B.4 Budget Impact: Per Treated Member Per Month (PTMPM):

| Cost outcomes | Current year | Year-1 | Year-2 | Year-3 |
|---|---|---|---|---|
| Cyclosporine A | | | | |
| Drug costs | $65.39 | $64.08 | $62.77 | $61.46 |
| Other costs | $4.17 | $4.09 | $4.00 | $3.92 |
| Total cyclosporine A costs | $69.55 | $68.17 | $66.77 | $65.38 |
| Methotrexate | | | | |
| Drug costs | $141.24 | $138.42 | $135.59 | $132.77 |
| Other costs | $6.50 | $6.38 | $6.25 | $6.12 |
| Total methotrexate costs | $147.74 | $144.80 | $141.85 | $138.89 |
| Mycophenolate mofetil | | | | |
| Drug costs | $21.97 | $21.53 | $21.09 | $20.65 |
| Other costs | $1.40 | $1.38 | $1.35 | $1.32 |
| Total mycophenolate mofetil costs | $23.37 | $22.91 | $22.44 | $21.97 |
| Azathioprine | | | | |
| Drug costs | $26.66 | $26.13 | $25.59 | $25.06 |
| Other costs | $1.40 | $1.38 | $1.35 | $1.32 |
| Total azathioprine costs | $28.06 | $27.50 | $26.94 | $26.38 |
| Dupilumab | | | | |
| Drug costs | $1,998.92 | $1,959.68 | $1,919.68 | $1,879.69 |
| Other costs | $7.61 | $7.49 | $7.34 | $7.19 |
| Total dupilumab costs | $2,006.52 | $1,967.17 | $1,927.02 | $1,886.88 |
| Upadacitinib | | | | |
| Drug costs | $0.00 | $115.00 | $230.00 | $345.00 |
| Other costs | $0.00 | $0.48 | $0.95 | $1.43 |
| Total upadacitinib costs | $0.00 | $115.48 | $230.95 | $346.43 |
| Total PTMPM costs | $2,275.26 | $2,346.02 | $2,415.98 | $2,485.93 |
| Incremental budget impact versus current market | | | | |
| Total PTMPM costs | - | $70.77 | $140.72 | $210.67 |

## B.5 Sensitivity Analysis:

| Parameter | Base Case | Variation | Minimum | Maximum |
|---|---|---|---|---|
| Atopic dermatitis prevalence | 4.90% | 95% CI | 4.60% | 5.20% |
| Moderate-to-severe atopic dermatitis prevalence | 40% | 95% CI | 33.90% | 46.40% |
| Upadacitinib treatment acquisition cost | $69,000 | ±50% | $34,499.80 | $103,499.40 |
| Cyclosporine A treatment acquisition cost | $7,846.33 | ±50% | $3,923.17 | $11,769.50 |
| Dupilumab treatment acquisition cost | $43,310 | ±50% | $21,655.00 | $64,965.00 |
| Methotrexate treatment acquisition cost | $8,475 | ±50% | $4,237.50 | $12,712.50 |
| Mycophenolate mofetil treatment acquisition cost | $5,273 | ±50% | $2,636.32 | $7,908.96 |
| Azathioprine treatment acquisition cost | $6,398 | ±50% | $3,199.23 | $9,597.68 |

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## VITA

Haya Alobaid graduated from the College of Pharmacy at King Saud University (Riyadh, Saudi Arabia) in 2018, obtaining her Bachelor of Science degree in Pharmaceutical Sciences with first honor of certificate. Haya had her training as a Pharmacist at King Fahad Medical City (KFMC) hospital in Riyadh, Saudi Arabia. Shortly after graduation, she started to work at SANOFI pharmaceutical company as a medical representative for cardiovascular and diabetic medications. In 2020, she joined the Department of Pharmacotherapy and Health Outcomes at Virginia Commonwealth University (Richmond, Virginia, United States) as a Master of Science student. Her research, under the supervision of Dr. David A. Holdford. Haya joined the Student Network of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) as a committee member and completed several courses regarding budget impact analysis (BIA) and health technology assessment (HTA).