VitalTransformation

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# Calculating the Value and Impact of Accelerated Approvals

November 15, 2022

## PREPARED BY


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# This research was made possible with the support of:

Bio Biotechnology Innovation Organization
GLOBAL CEOINITIATIVE ON ALZHEIMER'S DISEASE
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ALEXION AstraZeneca Rare Disease
Bristol Myers Squibb

# What is an Accelerated Approval?

- "In 1992, FDA instituted the *Accelerated Approval* regulations. These regulations allowed drugs for serious conditions that filled an unmet medical need to be approved based on a surrogate endpoint."
- "A surrogate endpoint … is a … laboratory measurement, radiographic image, physical sign, or other measure that … is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on irreversible morbidity and mortality (IMM)."

The Accelerated Approval (AA) pathway was implemented to help fight AIDs/HIV, and is considered a success in addressing areas of high unmet medical needs.

https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/accelerated-approval

# Overview – building the Accelerated Approval (AA) model

VitalTransformation

1. Vital Transformation extracted a cohort of all accelerated approvals from 2001 – 2021, both for primary (125) and secondary (81) indications that had not been withdrawn (N=206).

2. We estimated the median and quartiles of time it takes to confirm an FDA's accelerated approval for converted primary therapies (n=48), modeling the entire primary cohort (n = 93).

3. Clinical phase trial costs per drug (in constant 2013 USD) were adapted from Joseph A. DiMasi (et al.) and K. Jayasundara (et al.); annual revenues were measured in constant 2013 USDs using the CPI index; NPVs are calculated using a 11% real cost of capital.

4. We allow for 11 years of revenue starting from the AA year.

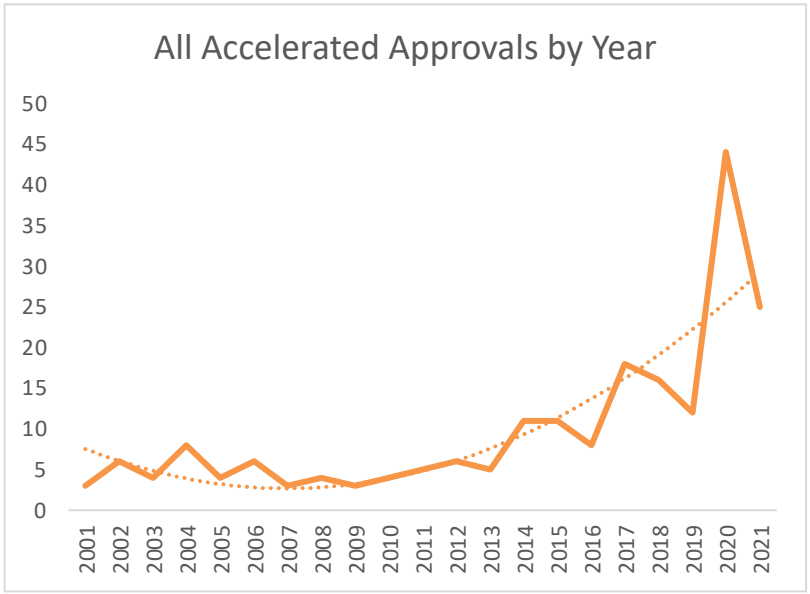
5. For therapies with no (future) revenue data, we predicted revenues by first estimating separate orphan/non-orphan revenue growth equations; the estimated growth rates where then applied using observed orphan/non-orphan mean revenue as the initial revenue value. NPVs were then computed assuming a 2, 3, 4, or 5-year delay for FDA approval.

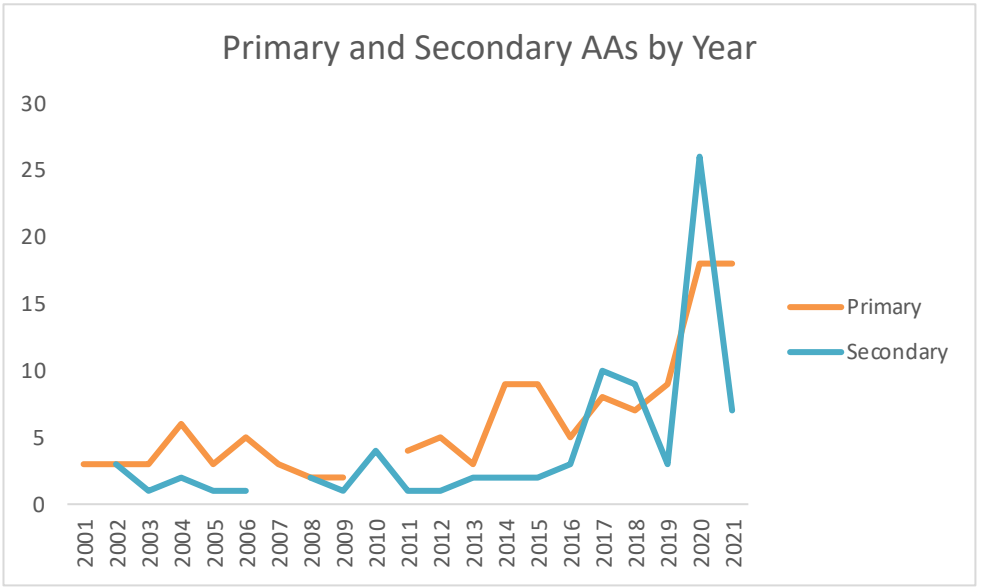
6. We estimate the impact of trial size and secondary indications on the profitability of an asset, which ultimately impacts covered-lives due to any potential lost therapies.

# Accelerated approvals – FDA and CMS

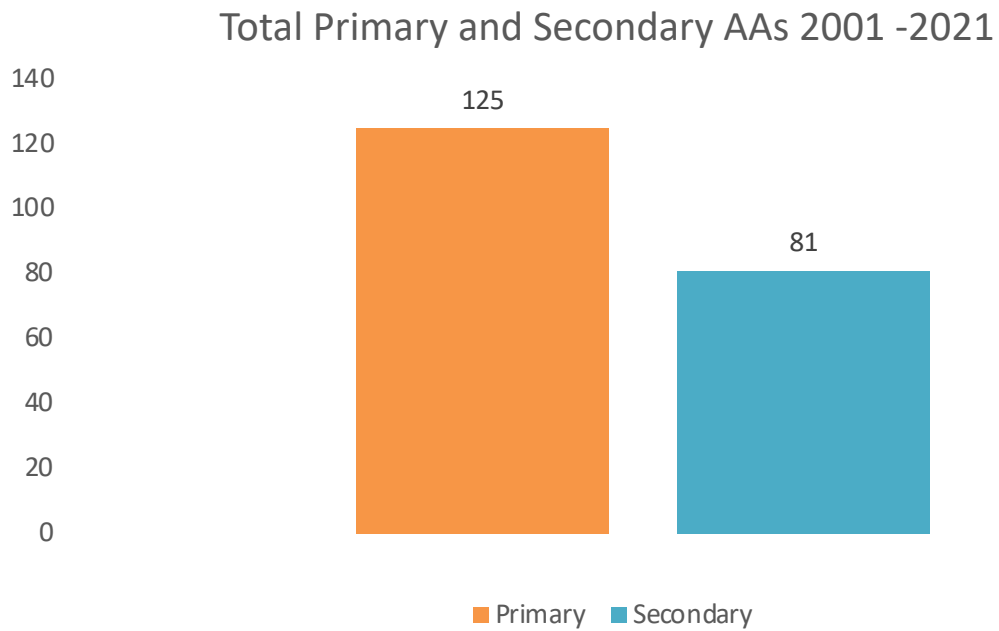
# Accelerated Approvals are increasing

2001 – 2021, n=206



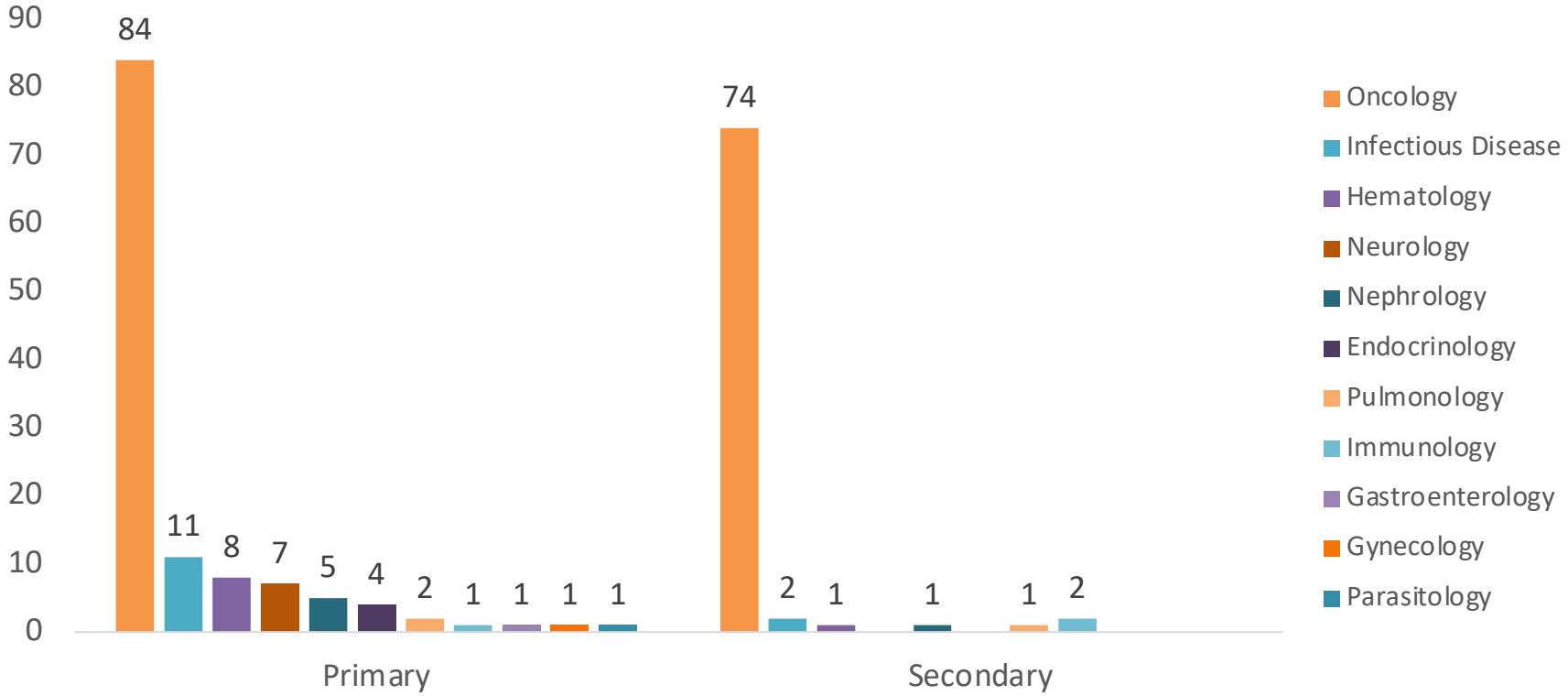



# Primary approvals are 60% of the cohort



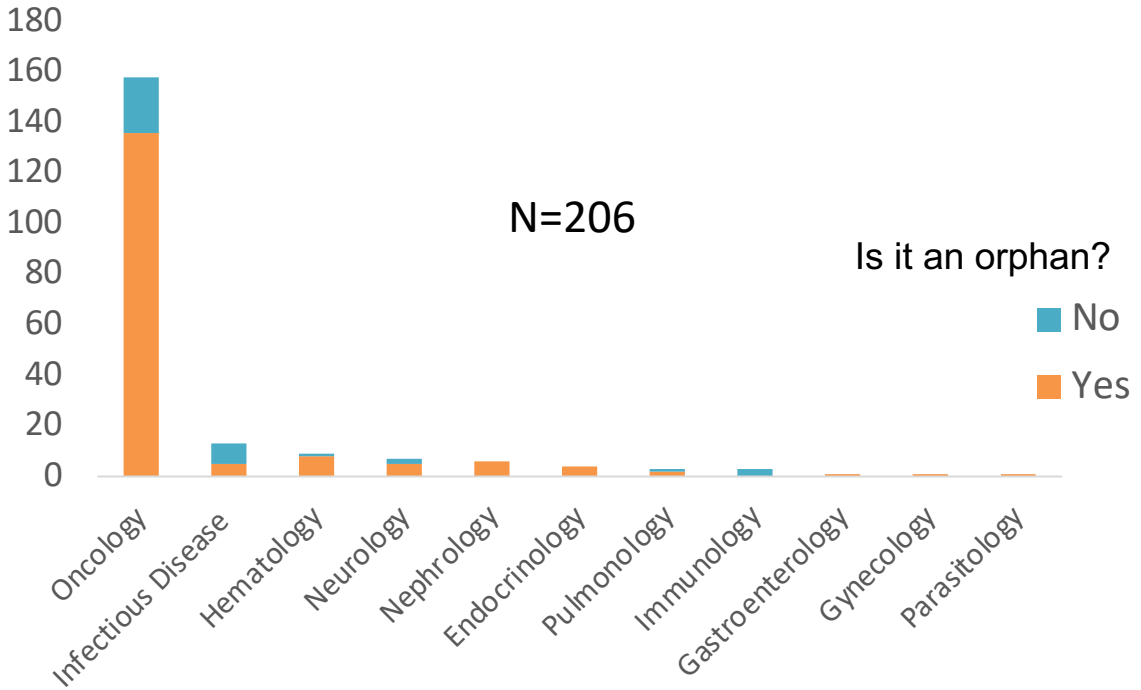
# Indications by approval type

N=206 (oncology = 158, non-oncology = 48)



# Orphan indications are 82% of our AA cohort

an orphan indication is < 200,000 persons in the US, 6 cases per 10,000




The use of surrogate endpoints in the accelerated approval pathway is often utilized for orphan indications.

# Merits of the accelerated approval pathway are under debate

**Scott Gottlieb criticizes CMS in feud over Aduhelm coverage, calls out their lack of expertise**

ENDPOINTS NEWS

Paul Schloesser
Associate Editor

"CMS is now using the issue of whether or not a drug is approved under regular approval versus accelerated approval as a basis potentially going forward for denying coverage to drugs."

FIERCE Pharma

"Robert Califf, President Joe Biden's pick for the top spot at the FDA, has snared the support of the Senate Finance Committee chairman thanks to a vague pledge to reform the agency's accelerated approval pathway if he's confirmed."

**Oregon Scraps Closed-Formulary Plan But Seeks To Deny Accelerated Approval Drugs**
By John Wilkerson / February 24, 2022 at 5:40 PM

InsideHealthPolicy
An Inside Washington news service

The Washington Times

**Oregon wants to ration health care in new proposal**

Government bureaucrats show their cards

"The state is seeking a federal waiver that would allow it to decline Medicaid coverage for some FDA -approved drugs… targeting medications on the… 'accelerated use' pathway"

# What is behind the debate?

There is growing sentiment from some payers, academics, and state and federal policymakers that the pathway needs to be significantly altered or restrictions applied to drugs approved through the accelerated approval pathway.

**Are these criticisms based in reality? Let's find out…**

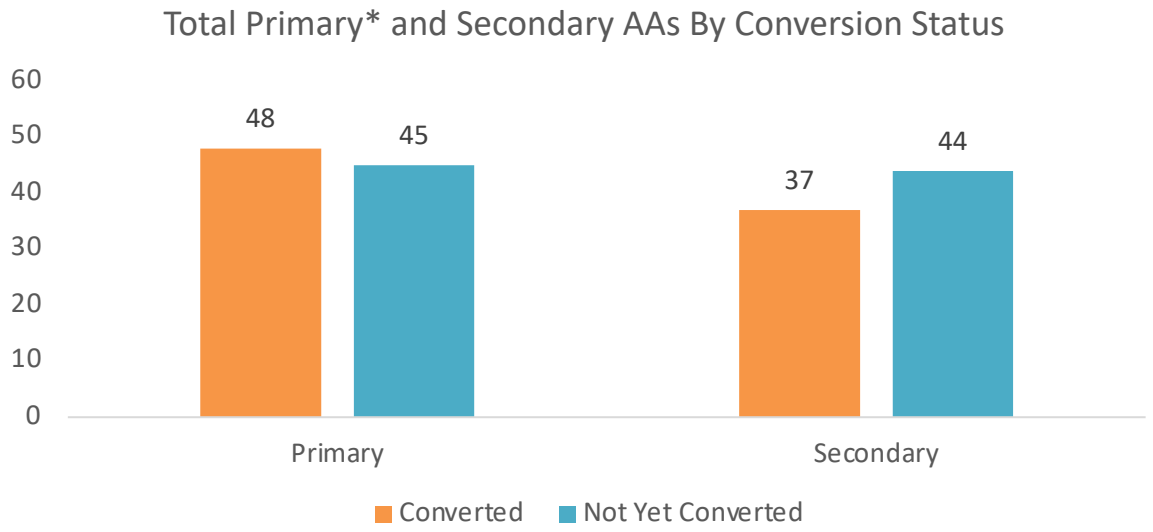
# Modeling the impact of changes to the accelerated approval

## what we did

Thesis: The net present value (NPV) of therapies will be negatively impacted by changes to the accelerated approval pathway that increases the time to market.

1. We used the total patients enrolled in the confirmed primary trials as reported to FDA as the basis of our trial cost calculations.
2. We calculated the average confirmatory trial cost per patient as defined by Jayasundara et al.
3. We scaled up the lower Jayasundara costs to DiMasi's trial costs (x 2.89), giving us two points of comparison for impacts (low and high).
4. We modeled the NPV of investing in each therapy in the entire primary cohort (n=93) assuming the confirmatory trial length was extended by 2, 3, 4, and 5 years before full FDA marketing approval was granted, hence delaying the time when sales are generated.
5. A negative NPV in our model for an approved drug means that it is unlikely it would have been developed if changes to the accelerated approval had been implemented at the time of the therapy's development.

# Our NPV analysis focuses on primary AAs



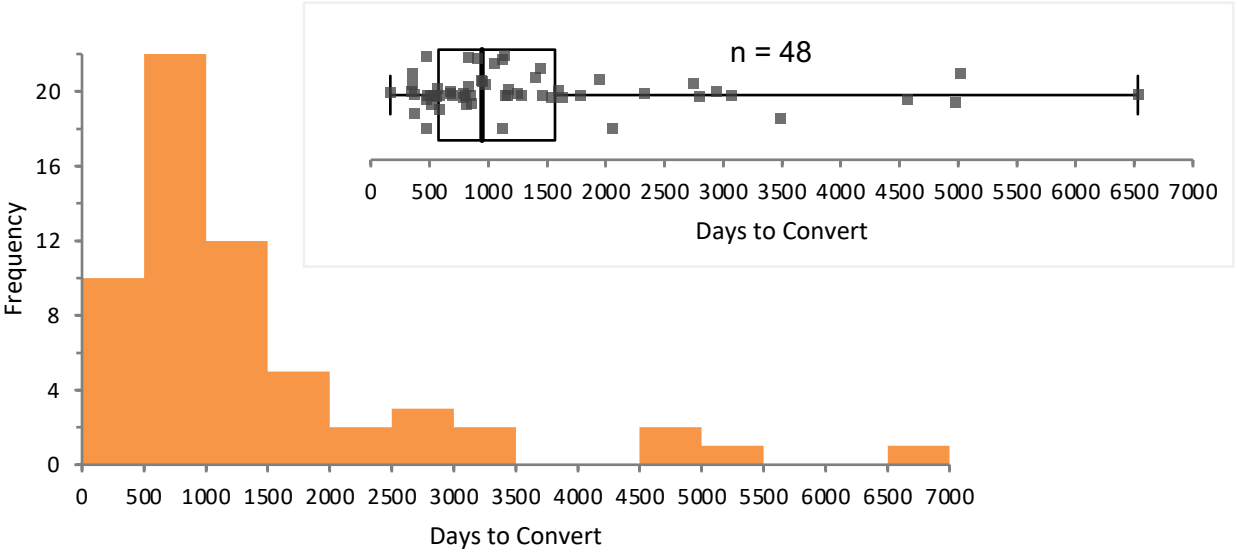

* Our 125 primary AAs are reduced by filtering those with multiple indications, repurposed off-patent therapies, and generics with AAs, leaving 93 therapies in our primary NPV cohort.

Drug companies are required to conduct phase 4 trials to confirm the anticipated clinical benefit of an AA drug. If the confirmatory trial shows that the drug provides the anticipated clinical benefit, then the FDA grants traditional approval for the drug, i.e., the drug is ***converted*** from an AA approval to a traditional FDA approval.

# Median years needed to submit confirmatory evidence (2001 – 2021)

i.e., FDA 'Conversion" from accelerated to traditional approval

| Conversion Time in Years | | | | |
|---|---|---|---|---|
| **Minimum** | **1st quartile** | **Median** | **3rd quartile** | **Maximum** |
| 0 | 2 | 3 | 4 | 18 |




The median time to convert from an accelerated to traditional approval is 3 years; 75% of all Accelerated Approvals convert within 4 years.

# Sources of the cost basis of our analysis

Research | Open Access | Published: 10 January 2019

## Estimating the clinical cost of drug development for orphan versus non-orphan drugs

Kavisha Jayasundara, Aidan Hollis, Murray Krahn, Muhammad Mamdani, Jeffrey S. Hoch & Paul Grootendorst

*Orphanet Journal of Rare Diseases* **14**, Article number: 12 (2019) | Cite this article

**28k** Accesses | **48** Citations | **51** Altmetric | Metrics

Journal of Health Economics

Volume 47, May 2016, Pages 20-33

## Innovation in the pharmaceutical industry: New estimates of R&D costs ☆

Joseph A. DiMasi [a], Henry G. Grabowski [b], Ronald W. Hansen [c]

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https://doi.org/10.1016/j.jhealeco.2016.01.012

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# Cost basis for our analysis

## Average cost of drug development by clinical phase
## 2013 cost base, $US Mil

| | Non - Orphans | | | | | Orphans | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Jayasundara | | DiMasi | | | Jayasundara | | DiMasi | | |
| P1 | $ | 20 | $ | 58 | P1 | $ | 13 | $ | 38 | |
| P2 | $ | 67 | $ | 194 | P2 | $ | 63 | $ | 183 | |
| P3 | $ | 247 | $ | 713 | P3 | $ | 61 | $ | 176 | |
| | **$** | **334** | **$** | **965** | | **$** | **137** | **$** | **397** | |

# Results

# A 3 Year Delay Leads to 35% – 65% of AAs Likely Not Being Developed

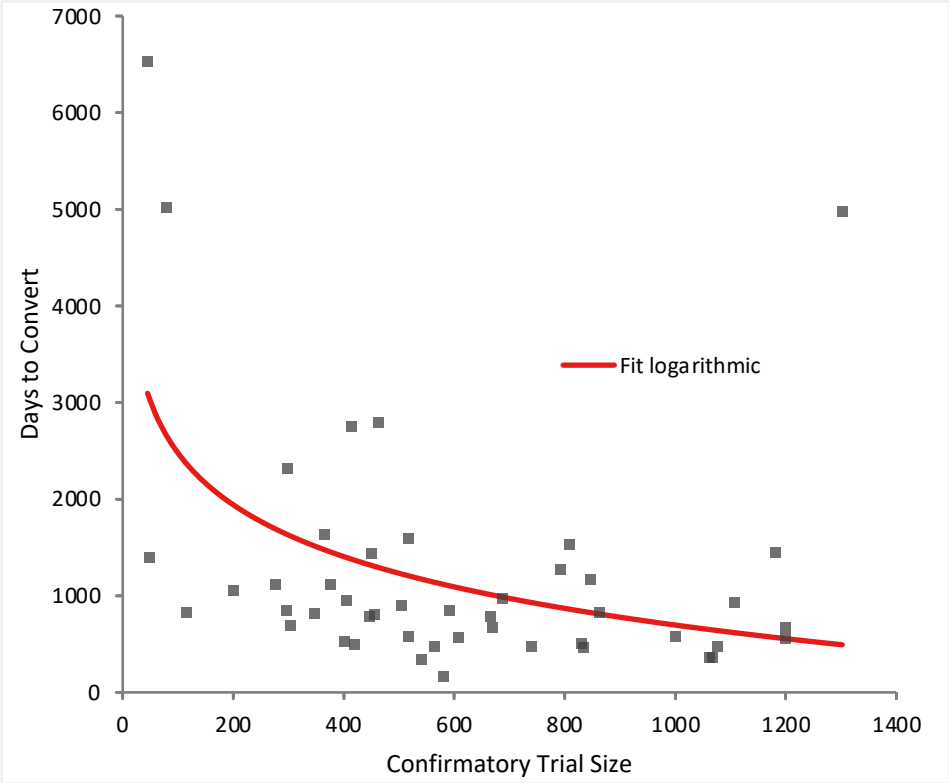
% of cohort with a negative NPV, n=93

| Cost Basis | 2 Year Delay | 3 Year Delay | 4 Year Delay | 5 Year Delay |
|---|---|---|---|---|
| Jayasundara | 28% | 35% | 41% | 51% |
| DiMasi | 54% | 65% | 68% | 73% |

- In general, a therapy with a negative NPV is unlikely to be brought to market or to even commence development since doing so would negatively impact a company's long-term value.
- If changes to the AA Pathway leads to a two-year delay in receiving FDA marketing approval, then 28% to 54% of the therapies in our cohort would exhibit a negative NPV.
- If removing AA Pathway leads to a five-year delay - which would encompass more than 80% of the AA therapies in our cohort – the percentage of therapies with a negative NPV would rise to between 51% and 73%.
- A negative NPV for an approved drug means that it is unlikely it would have been developed if changes to the accelerated approval had been implemented at the time of it's development.

# Larger, shorter trials are more likely to have a positive NPV

## Without an Accelerated Approval, smaller orphan therapies would struggle to come to market.



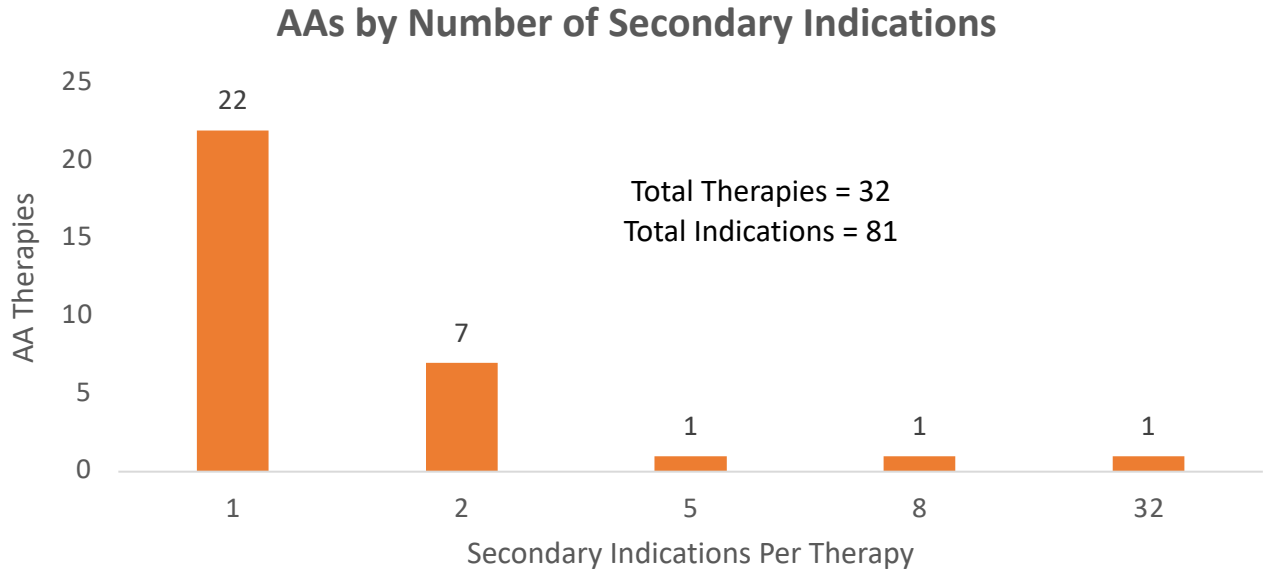

Most accelerated approvals are for orphan indications - our statistics show that the smaller the number of trial participants, the longer it takes to collect the required evidence. ($p < 0.001$, $R^2 = .22$)

Trial size and confirmatory trial length in our cohort shows that larger, shorter trials are statistically more likely to have a positive NPV ($p < 0.0004$, $R^2 = .16$)

The size of the confirmatory trial predicts the length of time required to fulfil FDA's evidence requirements and the likelihood of a drug being economically viable.

- Analysis excludes one clinical trial with 3360 subjects due to it being a significant outlier.

# The majority of AAs have only one secondary indication

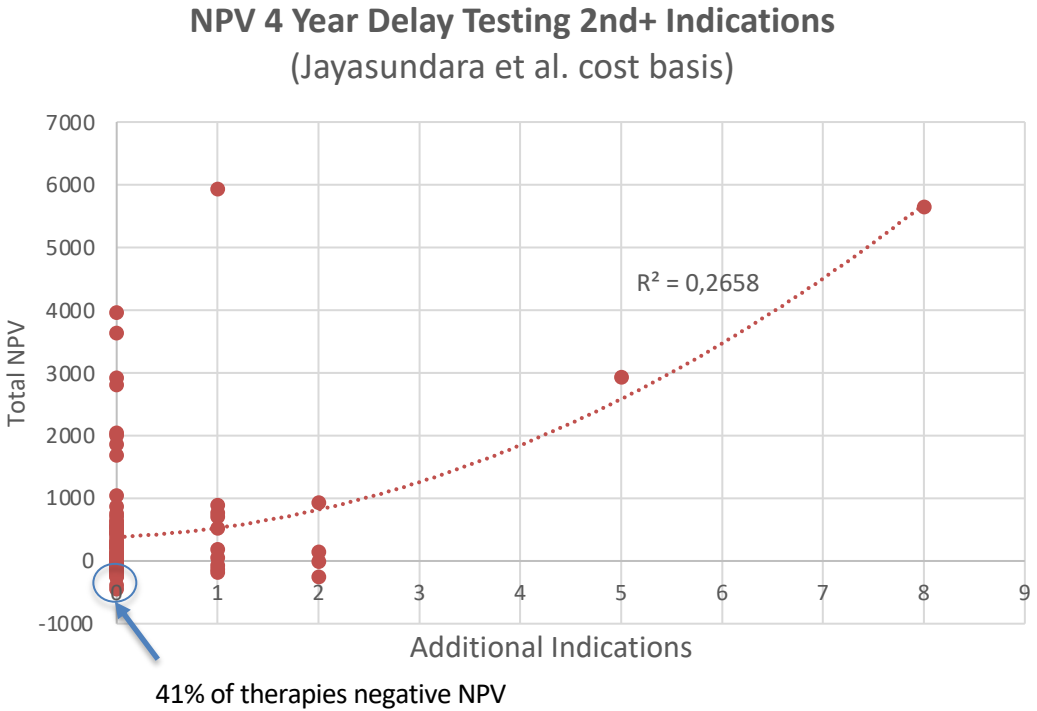



The therapies with the greatest number of secondary indications, in descending order, are Keytruda, Opdivo, and Gleevec.

All three are on the WHO's list of essential medicines and are highly effective late-stage oncology treatments.

# AA Pathway allows for additional indications to treat more patients with unmet needs

Keytruda as an outlier is removed




Additional indications are shown to predict a statistically significant rise in NPV.

Unfortunately, genetically targeted therapies don't have the opportunity for secondary indications.

Rather than being a negative, the data implies that extra indications can help ensure an overall positive NPV, thereby allowing the therapy to remain in the market to treat more patients with unmet medical needs.

$p < 0.0001$, N=93

# Implications for Patients and US Innovation

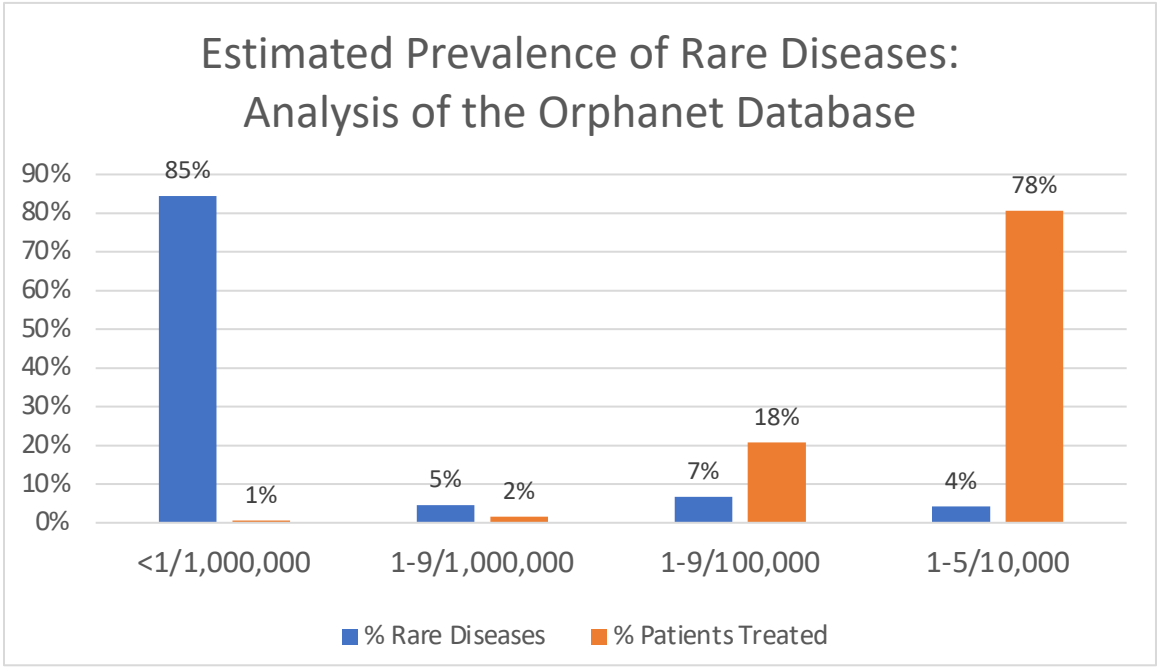
# A two to four year marketing delay due to changes to the AA Pathway negatively impacts 850,000 to 3.6 million patients

| Number of patients no longer covered if 2 year delay | | |
|---|---|---|
| **Clinical Area** | **Jayasundara** | **DiMasi** |
| Neurology | 123,090 | 1,226,082 |
| Oncology | 489,126 | 1,189,914 |
| Infectious Disease | 123,552 | 160,182 |
| Hematology | 100,287 | 100,287 |
| Endocrinology | 13,200 | 13,200 |
| Pulmonology | | 8,250 |
| **TOTAL** | **-849,255** | **-2,697,915** |

| Number of patients no longer covered if 4 year delay | | |
|---|---|---|
| **Clinical Area** | **Jayasundara** | **DiMasi** |
| Oncology | 910,602 | 1,942,413 |
| Neurology | 123,090 | 1,339,866 |
| Infectious Disease | 123,552 | 160,182 |
| Hematology | 100,287 | 111,177 |
| Endocrinology | 13,200 | 19,800 |
| Gastroenterology | | 13,200 |
| Pulmonology | | 8,250 |
| **TOTAL** | **-1,270,731** | **-3,594,888** |

- The above charts use US incidence rates to estimate the total number of covered lives that would lose access to therapies due to the indicated changes to the timing of the accelerated approval pathway.
- The chart shows total patients theoretically impacted by the withdrawal of therapies (by clinical area) that evidence a negative NPV under either a 2 or 4 year delay in traditional FDA approval.
- A 2 year delay impacts 28% of our accelerated approval cohort at minimum; a 4 year delay impacts for up to 68% of the therapies in our cohort.

# 85% of untreated orphan conditions have a prevalence of less than 1 in 1,000,000




Substantial changes to the accelerated approval pathway will likely render the potential development of therapies for most untreated orphan conditions economically untenable.

For 85% of orphan conditions currently lacking treatment in the US, each condition impacts a maximum of 330 people - an incidence rate less than 1/1,000,000.

https://www.nature.com/articles/s41431-019-0508-0

# Proposed accelerated approval changes at the state level

# Medicaid Provides Vital Therapies for Low-income Families and Children

Georgetown University Health Policy Institute
CENTER FOR CHILDREN AND FAMILIES

"About half of children in the United States (40 million) are now insured through Medicaid or the Children's Health Insurance Program (CHIP) — the vast majority in Medicaid."

"Medicaid plays a significant role in supporting the rare disease community… As of May 2021, Medicaid covers over 75.8 million Americans, making it the largest provider of health care coverage in the United States and a critical safety net for its enrollees."

NORD® National Organization for Rare Disorders

# States have proposed to reduce Medicaid access to Accelerated Approved therapies via 1115 waivers

"[States] have requested Section 1115 demonstration waivers. . .to exclude certain drugs… These states specifically requested authority to exclude coverage of accelerated approval drugs because state officials believe the high prices of these drugs do not lead to prudent fiscal administration when the clinical benefit has yet to be verified."

ENDPOINTS NEWS

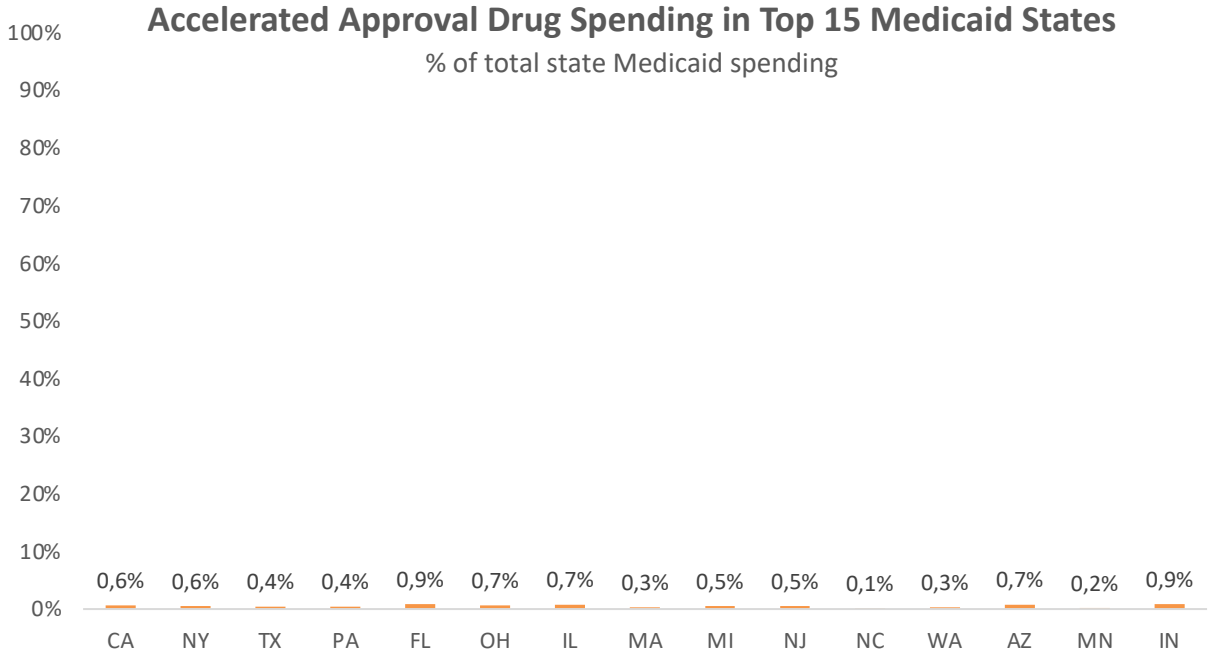
## Oregon's proposal was removed from CMS' final ruling

"CMS approved the Oregon Health Plan's 1115 Demonstration Waiver WITHOUT the provision that would have permitted the state to exclude coverage for prescription drugs approved using the accelerated approval pathway."

EVERYLIFE FOUNDATION FOR RARE DISEASES

# Budget impact of accelerated approval therapies on states is minimal

## the drugs in our cohort make up less than 0.5% of total Medicaid spending




- Accelerated approval therapies' relative impact on state Medicaid budgets is minimal.
- The average budget impact of AA therapies as a percentage of state Medicaid spending is one-half of one percent, 0.5%, across all 50 US states and DC.
- Given their limited weight in overall state budgets, but the enormous impact on patient access if AA therapies have delayed market entry, we question why 1115 waivers for these therapies would be deemed a priority.

# Impacts of delayed Medicaid access to accelerated approval therapies in US states

## Calculated by % of total Medicaid spending across all states (and DC)

| | Percent of therapies with negative NPV due to state delays to Medicaid entry | | | | | |
|---|---|---|---|---|---|---|
| | Jayasundara | | | DiMasi | | |
| % of states delayed | 3 yr delay | 4 yr delay | 5 yr delay | 3 year delay | 4 year delay | 5 year delay |
| 15% of states by spending | -18% | -23% | -30% | -42% | -46% | -51% |
| 25% of states by spending | -18% | -23% | -30% | -43% | -47% | -51% |
| 50% of states by spending | -19% | -23% | -31% | -43% | -47% | -51% |
| 75% of states by spending | -20% | -24% | -31% | -43% | -47% | -51% |
| 100% of states | -20% | -24% | -31% | -43% | -47% | -51% |

- **This is a retrospective analysis showing the impact on previously approved therapies if the restrictive Medicaid 1115 waivers had been in place at the time of their initial approval. Should this happen…**
  - A three-year delay in Medicaid access in 15% of states (by spending) resulted in 18% - 42% of our therapies having a negative NPV which would therefore render development unlikely.
  - Our research finds that targeted orphan indications are at higher risk from changes to the accelerated approval pathway, so it is likely that state Medicaid revenue reductions would have a greater impact on smaller orphan therapies.
  - A three-year delay in Medicaid access in 100% of states would result in 20% - 43% of our therapies having a negative NPV which would therefore render development unlikely.

# Patients no longer treated if 18% - 42% of therapies no longer come to market

estimated using US incidence rates per treatment in Medicaid

| | 3 Year Delay - Jayasundara Cost Basis | | | 3 Year Delay - DiMasi Cost Basis | | |
|---|---|---|---|---|---|---|
| **Indication** | **CA** | **MA** | **OR** | **CA** | **MA** | **OR** |
| Neurology | 0 | 0 | 0 | 147,488 | 25,810 | 15,486 |
| Oncology | 44,020 | 7,704 | 4,622 | 146,528 | 25,642 | 15,385 |
| Hematology | 12,000 | 2,100 | 1,260 | 13,320 | 2,331 | 1,399 |
| Infectious Disease | 10,280 | 1,799 | 1,079 | 10,280 | 1,799 | 1,079 |
| Gastroenterology | 0 | 0 | 0 | 1,600 | 280 | 168 |
| **Grand Total** | **66,300** | **11,603** | **6,962** | **319,216** | **55,863** | **33,518** |

- We have selected three states as case studies; MA and OR as they have considered 1115 exemptions, and CA as it is the largest consumer of Medicaid dollars.
- Using US incidence rates and the lower cost basis of Jayasundara, the median delay of 3 years in our example states results in roughly 85,000 patients losing access to treatments given our analysis of the potential loss of previously approved therapies.
- Using the DiMasi cost basis (regarded as more realistic), a 3-year delay indicates that neurology patients would be the most impacted by lost access, and the total number of patients who would have lost access to treatment rises to roughly 400,000.
- Given the small percentage of Medicaid spend on AA drugs relative to total state Medicaid spending, delaying access will only hurt patients with limited access to treatments for negligible budgetary gain.

# MACPAC Proposal
## Larger Price Reductions Specifically Targeting AA Therapies

- According to the MACPAC Report Addressing High-Cost Specialty Drugs, "The Congressional Budget Office (CBO) provided estimates assuming a 10 percentage point increase for the minimum rebate and a 20 percent increase in the inflationary rebate…"

- A 30% reduction in state Medicaid spending would result in an additional HIV therapy having a negative NPV, meaning it would no longer come to market.

- A 40% reduction in state Medicaid spending would result in an additional Oncology therapy having a negative NPV, meaning it would no longer come to market.

- Revenue reductions have the consequence of increasing risks for developers/investors – even though Medicaid therapies are highly discounted, large revenue reductions do increase the likelihood of fewer therapies being introduced to the market under the Accelerated Approval pathway.

# Conclusions

# Conclusions

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- If changes to the current FDA accelerated approval pathway occur, the predictions would result in a median delay of three years. This would result in a negative NPV for roughly 1/3rd to 2/3rds of accelerated approvals which would lead to a high-risk of not coming to market or even beginning development
- 82% of accelerated approvals are for orphan indications; our study generated evidence that smaller confirmatory trials take longer to meet their FDA requirements, larger and faster trials predict a positive NPV with statistical significance.
- 85% of untreated orphan indications have incidence rates less than 1/1,000,000; If changes to the accelerated approval pathway occur this could render the development of those therapies economically untenable.
- Developing secondary indications is a logical strategy to gain a positive NPV and retain a drug in the market - whereas Gleevec, Opdivo, and Keytruda have 2nd indications in Oncology, genetically targeted therapies have few opportunities for secondary indications.
- Possible changes to the AA pathway at the federal level put therapies at risk of withdrawal which would have addressed the needs of 850K to 3.6 mil patients, depending upon assumed costs and estimated delay times
- If changes to the current FDA accelerated pathway are made and a three-year delay occurs, we estimate that roughly 19%-43% of all accelerated approvals to no longer have a positive NPV and would therefore be at high-risk of not coming to market - especially if state Medicaid MACPAC rebates between 30%-40% were to become applied.
- Accelerated Approvals represent a small fraction of US States' overall Medicaid spending. Should a three-year delay come to fruition, between 66,000 and 319,000 state Medicaid program beneficiaries would lose access to new treatments with neurology and oncology being the most impacted.

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November 15, 2022

## PREPARED BY


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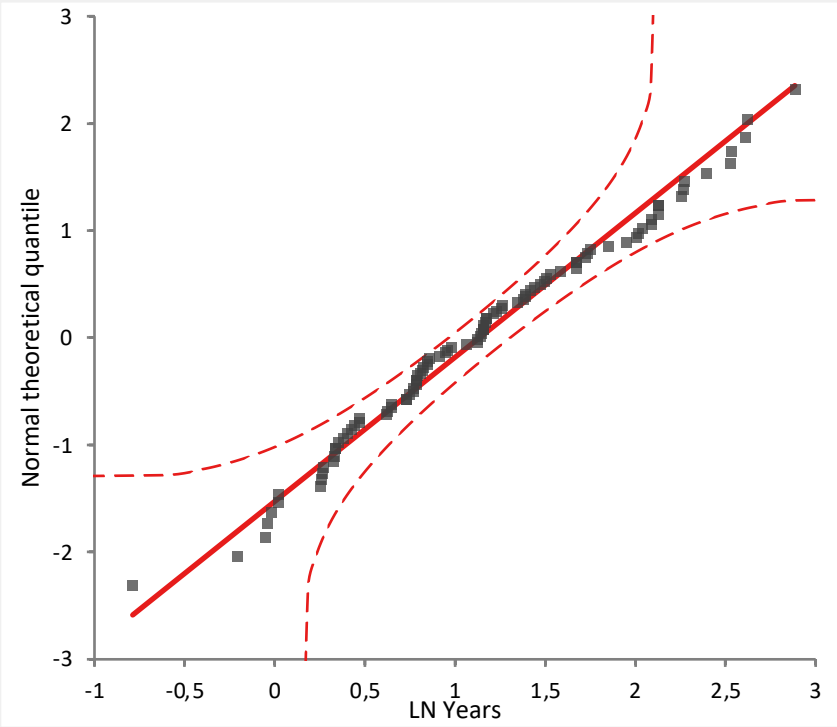
# Appendix:

# Ln Test for Normality All Converted (2001 – 2021)

## Primary approvals




Shapiro-Wilk test

| | |
|---|---|
| W statistic | 0.99 |
| p-value | 0.3787 |

H0: F(Y) = N(μ, σ)
The distribution of the population is normal with unspecified mean and standard deviation.
H1: F(Y) ≠ N(μ, σ)
The distribution of the population is not normal.
[1] Do not reject the null hypothesis at the 10% significance level.

# Regression results testing time to convert to confirmatory trial size

## Fit

| | |
|---|---|
| N | 47 |
| Mean of Y | 6.2 |

Equation: P3 Trial Size = 700.5 * 0.9997 $^{\text{Days to Convert}}$

| | |
|---|---|
| $R^2$ | 0.221 |
| $R^2$ adjusted | 0.203 |
| RMSE | 0.69 |

| Parameter | Estimate | 95% CI | SE | t | p-value |
|---|---|---|---|---|---|
| Constant | 6.552 | 6.266 to 6.837 | 0.14169 | 46.24 | <0.0001 |
| Days to Convert | -2.853E-04 | -4.462E-04 to -1.243E-04 | 7.9928E-05 | -3.57 | 0.0009 |

## Effect of Model

| Source | SS | DF | MS | F | p-value |
|---|---|---|---|---|---|
| Difference | 6.1 | 1 | 6.1 | 12.74 | 0.0009 |
| Error | 21.4 | 45 | 0.5 | | |
| Null model | 27.5 | 46 | 0.6 | | |

# Multiple Regression results testing size and length of confirmatory trial to NPV

| | |
|---|---|
| $R^2$ | 0.163 |
| $R^2$ adjusted | 0.144 |
| RMSE | 1839.568 |

| Parameter | Estimate | 95% CI | SE | t | p-value | VIF |
|---|---|---|---|---|---|---|
| Constant | 2090 | 814.7 to 3365 | 641.74 | 3.26 | 0.0016 | - |
| phase_3_length_years | -195.7 | -306.4 to -85.04 | 55.703 | -3.51 | 0.0007 | 1.06 |
| p3_trial_size | 0.7549 | -0.3895 to 1.899 | 0.57595 | 1.31 | 0.1933 | 1.06 |

| Source | SS | DF | MS | F | p-value |
|---|---|---|---|---|---|
| Difference | 5.860593E+07 | 2 | 2.930296E+07 | 8.66 | 0.0004 |
| Error | 3.011771E+08 | 89 | 3.384013E+06 | | |
| Null model | 3.597830E+08 | 91 | 3.953660E+06 | | |

# Regression output testing Jayasundara cost NPV to indication totals

```
------------------------------------------------------------------------------
                npv4 |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
---------------------+--------------------------------------------------------
secondary_indications |    523.641   100.1612     5.23   0.000     324.6533    722.6288
               _cons |   322.7092   111.9837     2.88   0.005     100.2341    545.1843
------------------------------------------------------------------------------

      Source |       SS           df       MS      Number of obs   =        92
-------------+----------------------------------   F(1, 90)        =     26.17
       Model |  13928422.2         1  13928422.2   Prob > F        =    0.0000
    Residual |  47904652.8        90   532273.92   R-squared       =    0.2253
-------------+----------------------------------   Adj R-squared   =    0.2167
       Total |  61833074.9        91   679484.34   Root MSE        =    729.57

------------------------------------------------------------------------------
                npv5 |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
---------------------+--------------------------------------------------------
secondary_indications |   364.9891   71.35042     5.12   0.000      223.239    506.7392
               _cons |   168.9939    79.7722     2.12   0.037     10.51249    327.4753
------------------------------------------------------------------------------
```