

ALIGNING DRUG DEVELOPMENT WITH MARKET NEED FOR **TNT BIO'S SUCCESS IN ATOPIC DERMATITIS AND BEYOND**

Team Go the Social Distance



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M.S in Education



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3rd Year PhD Bioengineering



| Eric Dai |
4th Year PhD Bioengineering

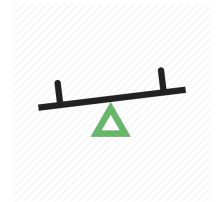
Ensuring Success for TNT Bio



Finding a
market need



Maximizing profits
within 15 years



Leveraging
profitable
co-indications

TNT Bio Strategy for Success

Goals

Finding a market need

Maximizing profits within 15 years

Leveraging profitable co-indications

Implementation

Estimate market size by patient segment

R&D and Capital Expenditure Offset by Drug Revenues





Evaluate Markets for Co-indications and Determine Profitability

Recommendation

We recommend that TNT Bio pursue **TNT-002** for AD and other indications

TNT-002 Has Greater Opportunity for AD Treatment



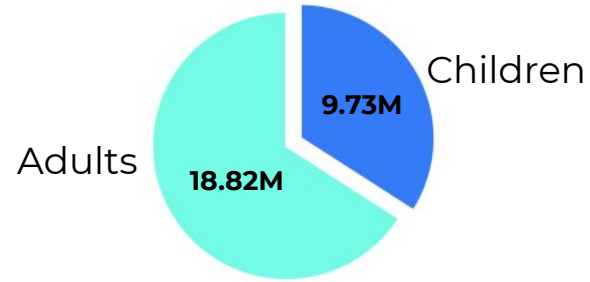
-  **TNT Bio's Options**
-  Product Comparison
-  Product Choice
-  Future Considerations

Atopic Dermatitis (AD) has High Potential for Market Growth



Global Market Size: \$10.4B
CAGR: 8.2% (2017-2023)

AD Patient Segments in U.S.

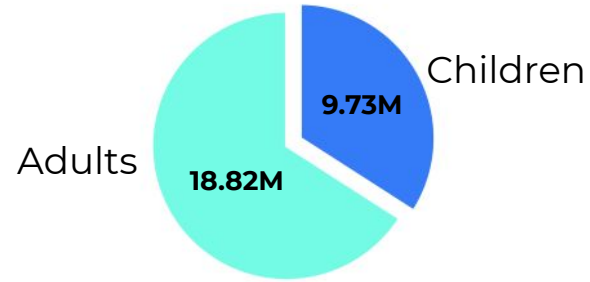


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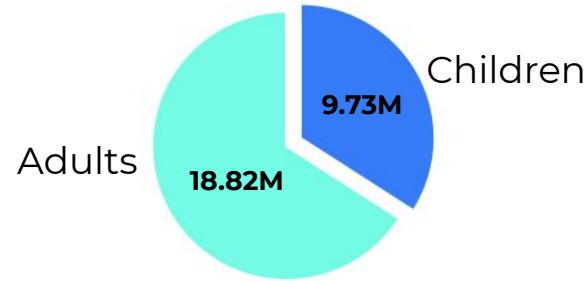
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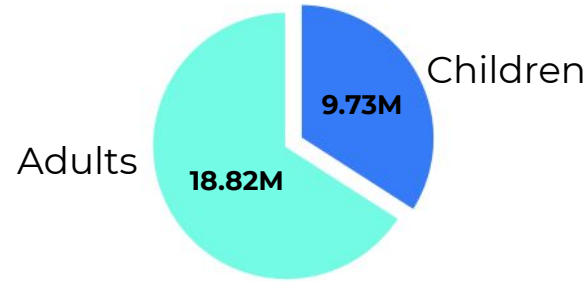
- 1** | Most traditional AD therapies fail to specifically target molecular mechanisms of pathogenesis
- 2** | **Children make up large patient segment but lack effective therapeutics for moderate-severe AD**

Atopic Dermatitis (AD) has High Potential for Market Growth



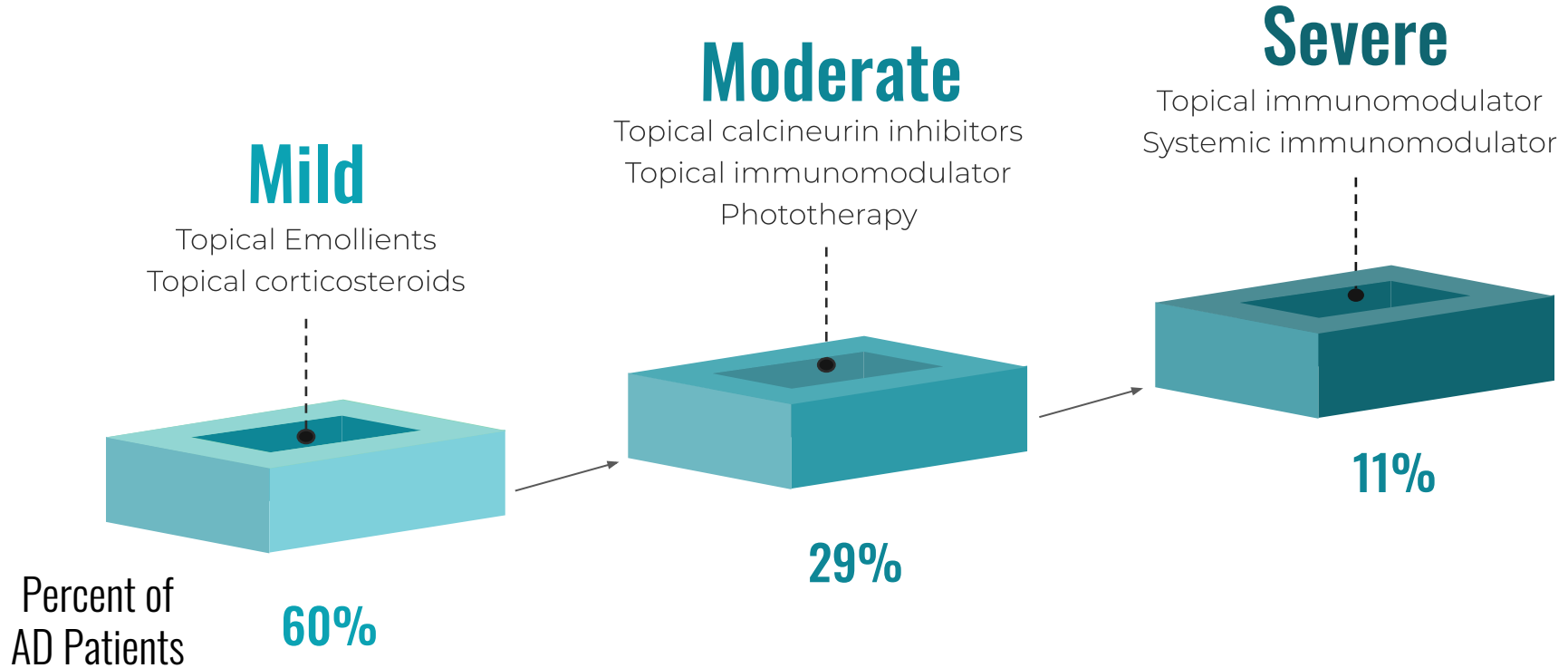
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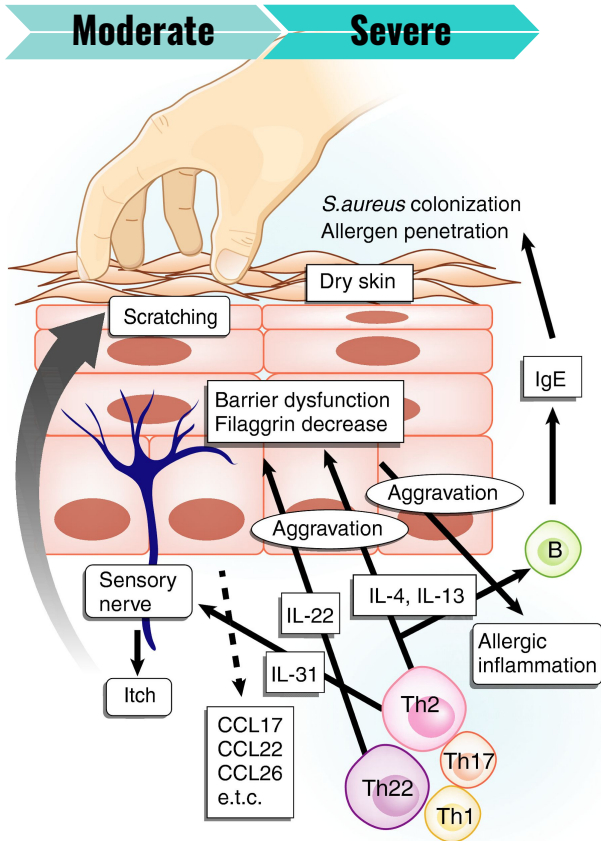


- 1** Most traditional AD therapies fail to specifically target molecular mechanisms of pathogenesis
- 2** Children make up large patient segment but lack effective therapeutics for moderate-severe AD
- 3** **Most systemic drugs have renal, hepatic, and other toxicities**

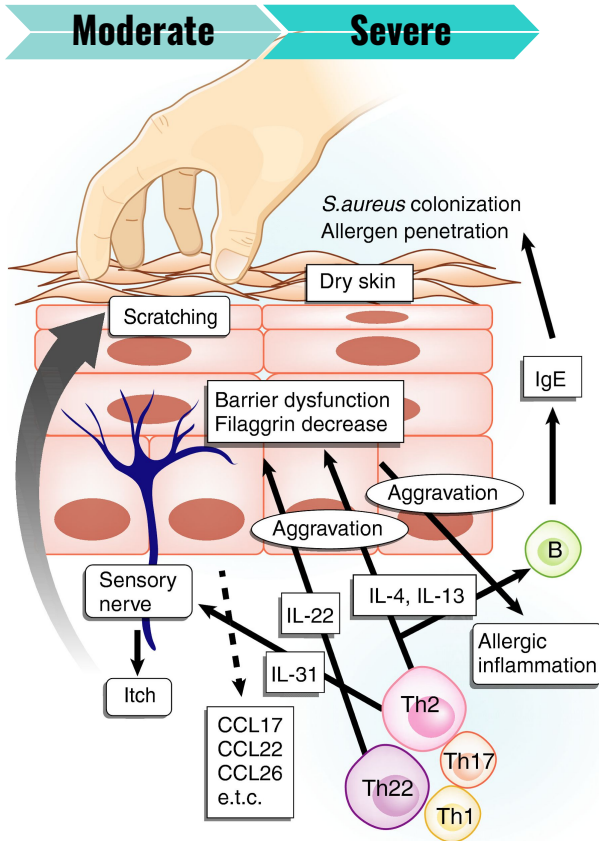
Line of Care for **AD** is Based on Severity of Symptoms



The Standard of Care for **Severe AD** is Inadequate

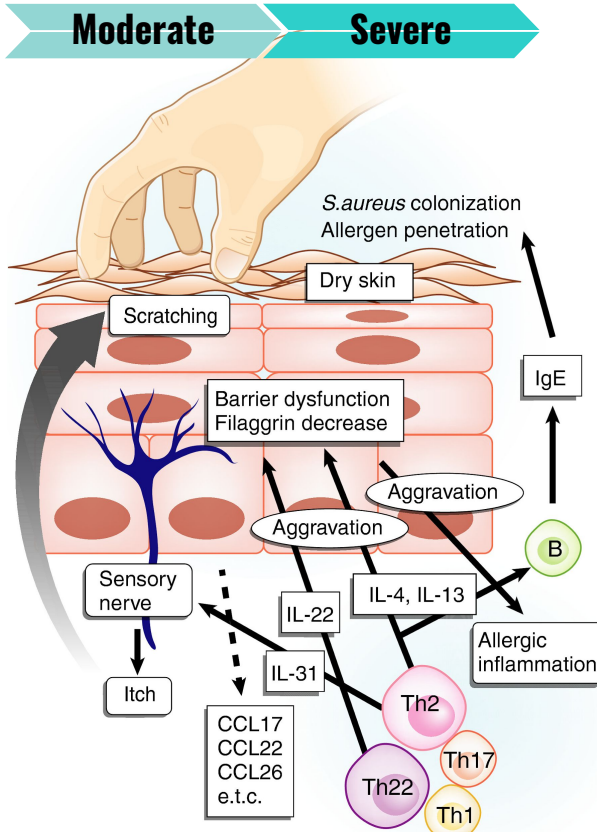


The Standard of Care for **Severe AD** is Inadequate



Require targeted therapy with:
↑ **Efficacy**
↓ **Off-target effects**

The Standard of Care for **Severe AD** is Inadequate



Require targeted therapy with:

- ↑ Efficacy
- ↓ Off-target effects

TNT Bio's Targeted Immunotherapy Products

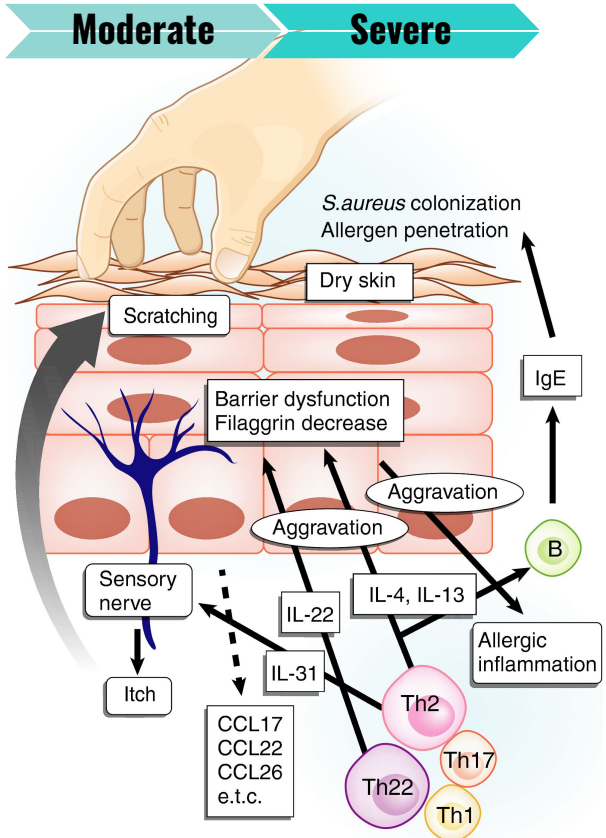
TNT-002

Topical TYK2 inhibitor

TNT-013

Anti-IL-13 Monoclonal Antibody Injection

The Standard of Care for **Severe AD** is Inadequate

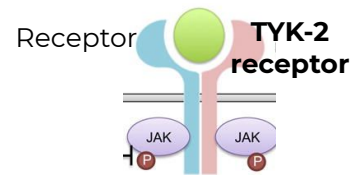


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TNT Bio's Targeted Immunotherapy Products

TNT-002

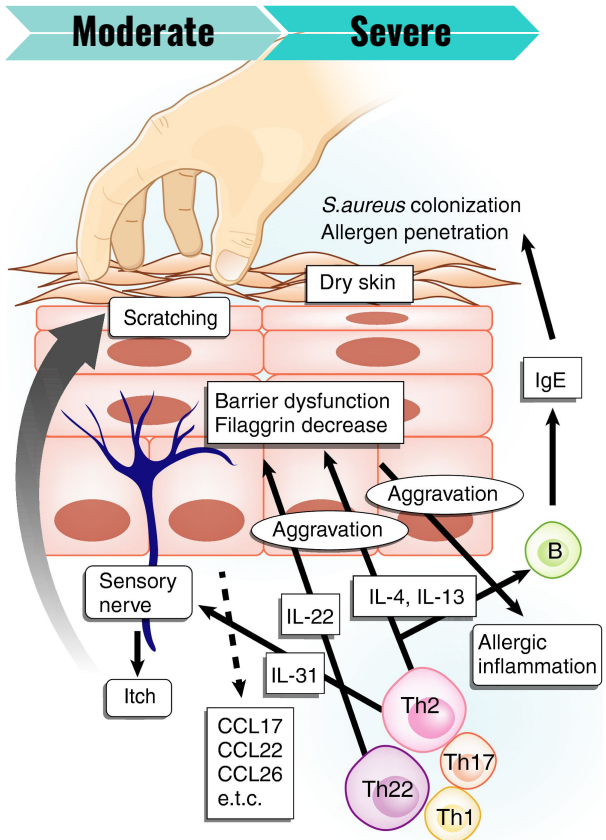
Topical TYK2 inhibitor
 ↓
 Locally blocks **multiple** inflammatory molecules
 IL-12, IL-13, IL-23, IFN α / β / λ
 Cytokines



TNT-013

Anti-IL-13 Monoclonal Antibody Injection

The Standard of Care for **Severe AD** is Inadequate



Require targeted therapy with:

- ↑ **Efficacy**
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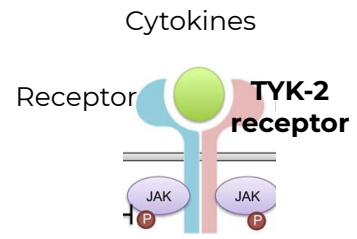
TNT Bio's Targeted Immunotherapy Products

TNT-002

Topical TYK2 inhibitor

Locally blocks **multiple** inflammatory molecules

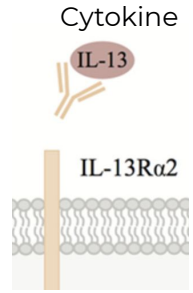
IL-12, IL-13, IL-23, IFN α / β / λ



TNT-013

Anti-IL-13 Monoclonal Antibody Injection

Systemically blocks a **single** inflammatory molecule



Source: Brunner et. al. 2017 J Allergy Clin Immun

The Standard of Care for Severe AD is Inadequate

Moderate

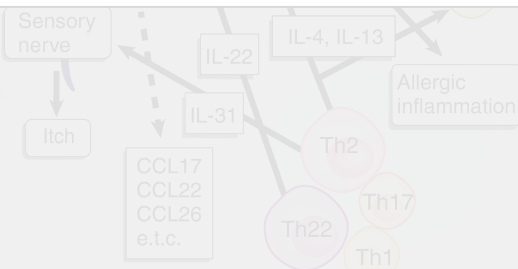
Severe

TNT Bio's Targeted Immunotherapy Products

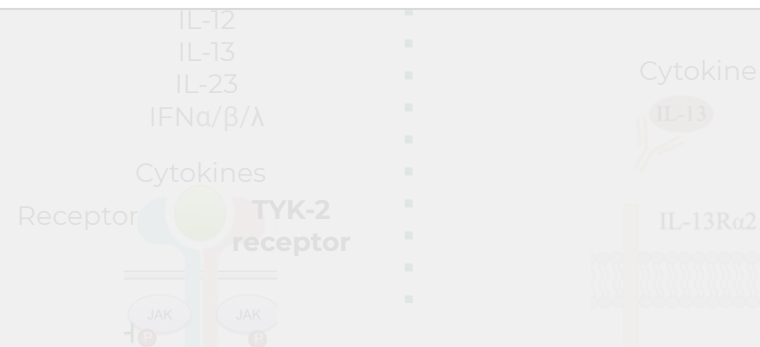
TNT-002

TNT-013

TNT Bio is positioned to enter **the moderate-to-severe AD market** to provide effective therapies with minimal off-target effects.







effects



TNT-002 Has Greater Opportunity for AD Treatment



-  TNT Bio's Options
-  **Product Comparison**
-  Solution
-  Future Considerations

Product Comparison is Based on 7 Factors

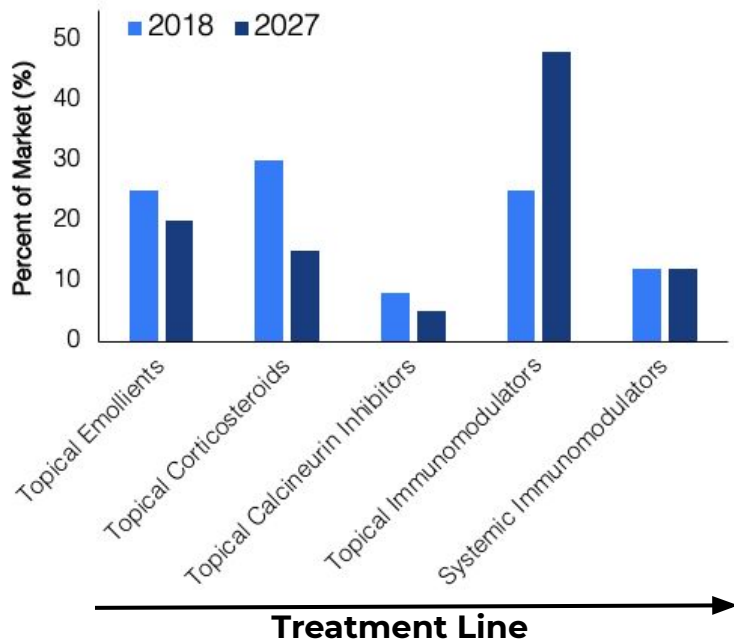
Factors
Market Size
Ease of Manufacturing
Low Risk for Off-target Effects
Competitive Landscape
Financial Justification
Co-indications
Regulatory Environment
OVERALL CHOICE

Product Comparison is Based on 7 Factors

Factors
Market Size
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OVERALL CHOICE

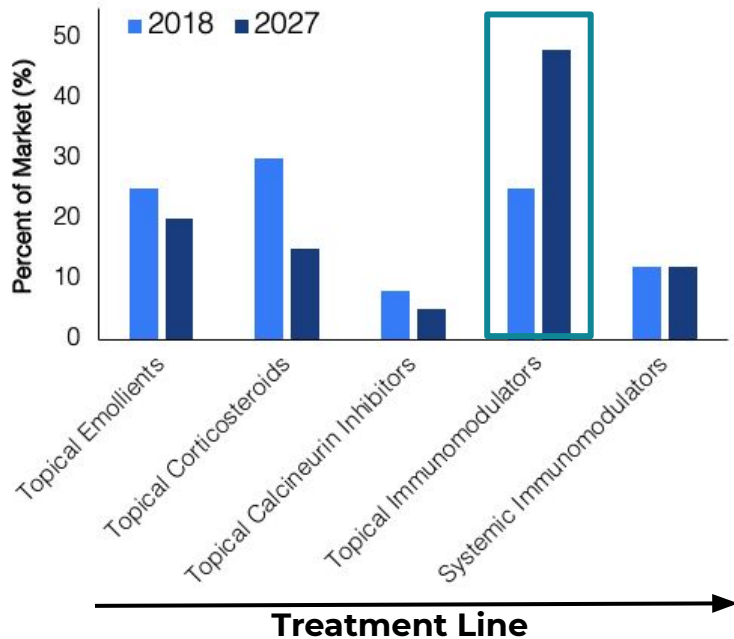
TNT-002 Will Capture Larger AD Patient Segments

AD Treatments and Projections



TNT-002 Will Capture Larger AD Patient Segments

AD Treatments and Projections



Targeted Immunotherapy

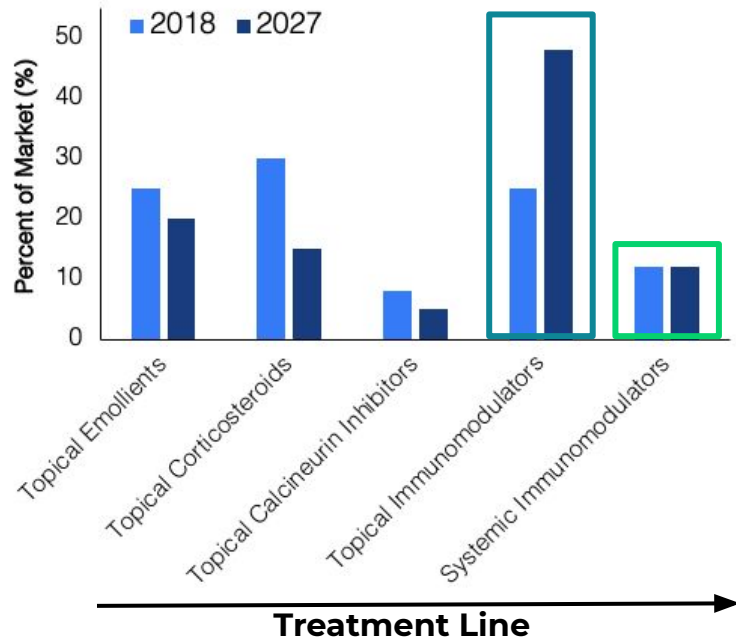
TNT-002

Topical



TNT-002 Will Capture Larger AD Patient Segments

AD Treatments and Projections



Targeted Immunotherapy

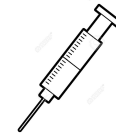
TNT-002

Topical



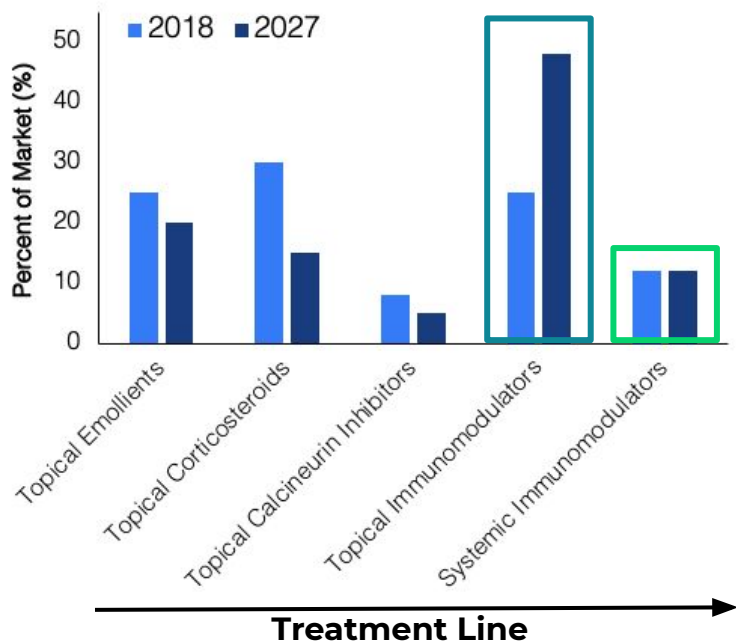
TNT-013

Systemic



TNT-002 Will Capture Larger AD Patient Segments

AD Treatments and Projections



Targeted Immunotherapy

TNT-002

Topical



All patients

2018: 7.13M

2027: 14.27M

TNT-013

Systemic



Adults only

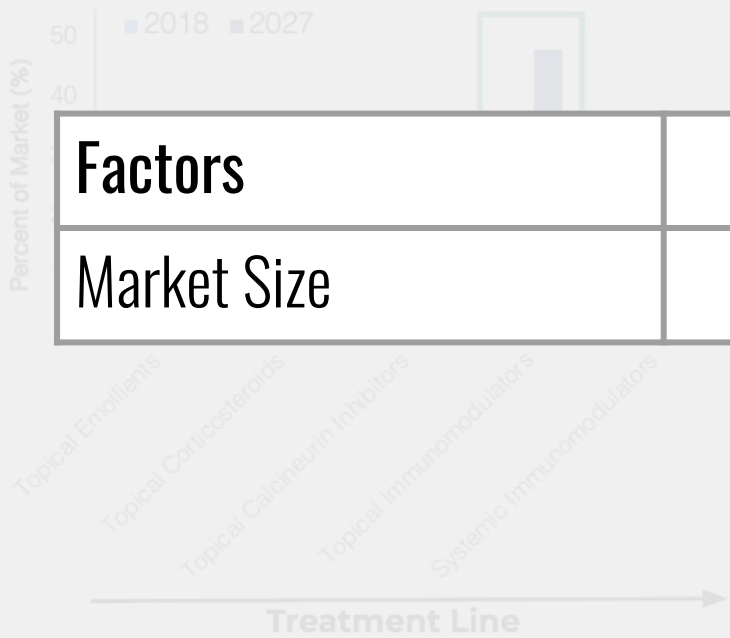
2018: 1.88M

2027: 1.88M

U.S.
Market

TNT-002 Will Capture Larger AD Patient Segments

AD Treatments and Projections



Allergen-specific Immunotherapy

TNT-002
Topical

TNT-013
Systemic

Factors	TNT-002	TNT-013
Market Size	✓	

All patients
2018: 7.13M
2027: 14.27M

Adults only
2018: 1.88M
2027: 1.88M

U.S. Market

TNT-002 Has Greater Opportunity for AD Treatment

Factors	TNT-002	TNT-013
Market Size	✓	
Ease of Manufacturing		
Low Risk for Off-target Effects		
Competitive Landscape		
Financial Justification		
Co-indications		
Regulatory Environment		
OVERALL CHOICE		

TNT-002 Development is Less Costly and Complex

TNT-002

Small Molecule



TNT-013

Monoclonal Antibody

TNT-002 Development is Less Costly and Complex

TNT-002

Small Molecule

- ✓ **Less complex production**
 - Simple, defined structure
 - Stable structure

TNT-013

Monoclonal Antibody



TNT-002 Development is Less Costly and Complex

TNT-002

Small Molecule

✓ **Less complex production**

- Simple, defined structure
- Stable structure

✓ **Low cost**

- Chemical synthesis
- Identical copies

TNT-013

Monoclonal Antibody

TNT-002 Development is Less Costly and Complex

TNT-002

Small Molecule

✓ Less complex production

- Simple, defined structure
- Stable structure

✓ Low cost

- Chemical synthesis
- Identical copies

TNT-013

Monoclonal Antibody

✗ Highly complex production

- Complex, less defined structure
- Sensitive to external conditions

TNT-002 Development is Less Costly and Complex

TNT-002

Small Molecule

✓ Less complex production

- Simple, defined structure
- Stable structure

✓ Low cost

- Chemical synthesis
- Identical copies

TNT-013

Monoclonal Antibody

✗ Highly complex production

- Complex, less defined structure
- Sensitive to external conditions

✗ High cost

- Living cell-reliant process
- Variable production


TNT-002 Development is Less Costly and Complex

TNT-002

Small Molecule

TNT-013

Monoclonal Antibody

Factors	TNT-002	TNT-013
Manufacturing		

Low cost

- Chemical synthesis
- Identical copies

High cost

- Living cell-reliant process
- Variable production

TNT-002 Has Greater Opportunity for AD Treatment

Factors	TNT-002	TNT-013
Market Size	✓	
Ease of Manufacturing	✓	
Low Risk for Off-target Effects		
Competitive Landscape		
Financial Justification		
Co-indications		
Regulatory Environment		
OVERALL CHOICE		

TNT-002 Has Greater Risk for Off-Target Effects

TNT-002

TYK2 inhibitor

x Affects multiple molecules

- Could interact with unintended targets
- Greater risk for off-target effects



TNT-002 Has Greater Risk for Off-Target Effects

TNT-002

TYK2 inhibitor

x Affects multiple molecules

- Could interact with unintended targets
- Greater risk for off-target effects

TNT-013

IL-13 Monoclonal Antibody

✓ Affects one molecule

- Specifically targets a single cytokine, IL-13
- Reduced risk for off-target effects


TNT-002 Has Greater Risk for Off-Target Effects

TNT-002

Small Molecule

TNT-013

Monoclonal Antibody

Factors	TNT-002	TNT-013
Less Risk for Off-target Effects		

unintended targets

- Greater risk for off-target effects

TNT-002 Has Greater Opportunity for AD Treatment

Factors	TNT-002	TNT-013
Market Size	✓	
Ease of Manufacturing	✓	
Low Risk for Off-target Effects		✓
Competitive Landscape		
Financial Justification		
Co-indications		
Regulatory Environment		
OVERALL CHOICE		

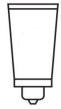
TNT-002 Has Less Competition in the AD Market

Phase I

Phase II

Phase III

In the Market



TNT Bio: **TNT-002**

Mechanism of Action:
TYK2 Inhibition (Topical)

TNT-002 Has Less Competition in the AD Market

Phase I



TNT Bio: **TNT-002**

Mechanism of Action:
TYK2 Inhibition (Topical)

Phase II

Phase III


olumiant.
(baricitinib) tablets
2 mg

Eli Lilly: **Olumiant**

Comparable Mechanism of Action:
JAK1/2 Oral Inhibitor



Pfizer: **Abrocitinib**

Comparable Mechanism of Action:
JAK1 Oral Inhibitor


RINVOQ™
upadacitinib 15mg tablets

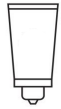
Abbvie: **Rinvog**

Comparable Mechanism of Action:
JAK1 Oral Inhibitor

In the Market

TNT-002 Has Less Competition in the AD Market

Phase I



TNT Bio: **TNT-002**

Mechanism of Action:
TYK2 Inhibition (Topical)



Competitive Advantage:
Only **topical inhibitor** that
targets TYK2 in JAK/STAT
pathway

Phase II

Phase III


olumiant.
(baricitinib) tablets
2 mg

Eli Lilly: **Olumiant**

Comparable Mechanism of Action:
JAK1/2 Oral Inhibitor



Pfizer: **Abrocitinib**

Comparable Mechanism of Action:
JAK1 Oral Inhibitor


RINVOQ™
upadacitinib 15mg
tablets

Abbvie: **Rinvog**

Comparable Mechanism of Action:
JAK1 Oral Inhibitor

In the Market

TNT-013 has steep competition in AD

Phase I



TNT Bio: **TNT-013**

Mechanism of Action:
IL-13 Inhibition (Injection)

Phase II

Phase III



Leo Pharma: **Tralokinumab**

Comparable Mechanism of Action:
IL-13 Inhibition (Injection)



Dermira: **Lebrikizumab**

Comparable Mechanism of Action:
IL-13 Inhibition (Injection)

In the Market



FDA Approved for AD:
March 2017 (adults) and
March 2019 (adolescents)

Comparable Mechanism of Action: Blocks IL-4 and IL-13 via IL-4R α inhibition

Strong Sales: Revenues of over \$2.2 B in 2019, with projected growth up to \$10 B

TNT-013 has steep competition in AD

Phase I

Phase II

Phase III

In the Market



Asana BioSciences:
A-1000



Leo Pharma: Trelekinumab



TNT Bio

Mechan
IL-13 Inh

Factors

TNT-002

TNT-013

Competitive Landscape



AD:
(s) and
(scents)



Dermira: Lebrikizumab

Comparable Mechanism of Action:
IL-13 Inhibition (Injection)

Comparable Mechanism of Action: Blocks IL-4 and IL-13 via IL-4R α inhibition

Strong Sales: Revenues of over \$2.2 B in 2019, with projected growth up to \$10 B

TNT-002 Has Greater Opportunity for AD Treatment

Factors	TNT-002	TNT-013
Market Size	✓	
Ease of Manufacturing	✓	
Low Risk for Off-target Effects		✓
Competitive Landscape	✓	
Financial Justification		
Co-indications		
Regulatory Environment		
OVERALL CHOICE		

TNT-002 Will Generate Higher Revenues Faster

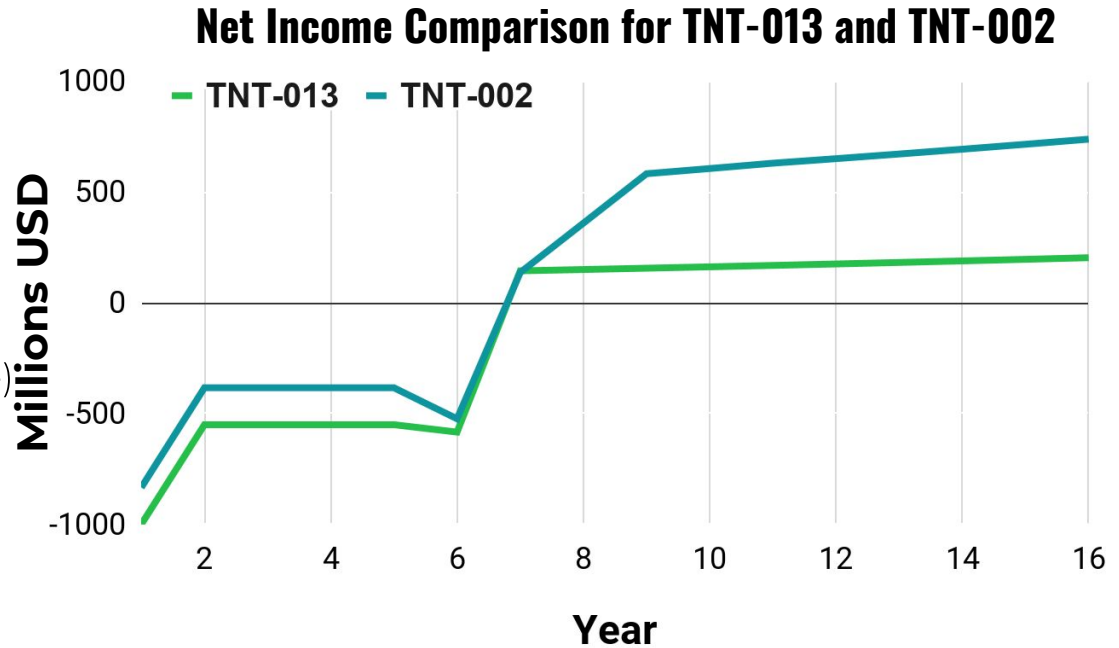
Model Assumptions

- Market Launch in 2027 (Clinical Trial period of 7 years)
- 1% Penetration Rate
- **TNT-013**
 - \$3B R&D Cost
 - \$37,000/yr (Dupilumab price)
 - 1.88MM customer base
- **TNT-002**
 - \$2B R&D Cost
 - \$10,000/yr (Eucrisa pricing)
 - 14.25MM customer base

TNT-002 Will Generate Higher Revenues Faster

Model Assumptions

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TNT-002 Has a Shorter Payback Period

	<u>Payback Period</u>	<u>IRR</u>
<u>TNT-002</u>	~4.6 Years	+8.11%
<u>TNT-013</u>	~24 Years	+8.53%

TNT-002 Has Shorter Payback Period

Payback Period

IRR

Factors	TNT-002	TNT-013
Financial Justification	✓	

TNT-013

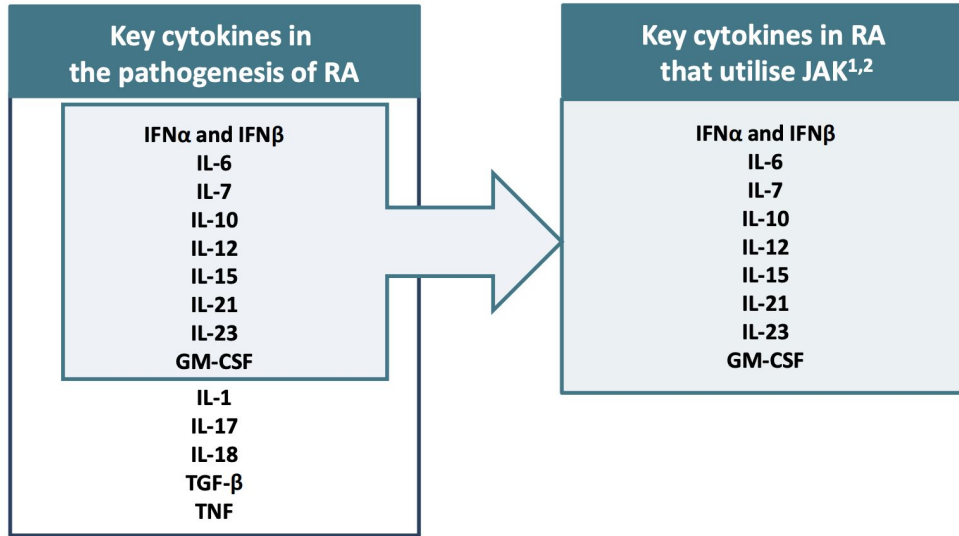
~24 Years

+8.53%

TNT-002 Has Greater Opportunity for AD Treatment

Factors	TNT-002	TNT-013
Market Size	✓	
Ease of Manufacturing	✓	
Low Risk for Off-target Effects		✓
Competitive Landscape	✓	
Financial Justification	✓	
Co-indications		
Regulatory Environment		
OVERALL CHOICE		

TNT-002 Shows Promise for Rheumatoid Arthritis (RA)



JAK Inhibitors Target and Stage of Development for RA

Compound	Primary Target(s)	Stage of Development
Tofacitinib	JAK3/JAK1>>JAK2	Approved by FDA and others at 5 mg BID and XR at 11 mg QD
Baricitinib	JAK1>JAK2	Approved by FDA at 2 mg QD Approved by EMA and others at 2 mg and 4 mg QD
Upadacitinib	JAK1>>JAK3	Approved by FDA at 15 mg QD
Filgotinib	JAK1>>JAK2	Phase 3

FDA, US Food and Drug Administration; EMA, European Medicines Agency; MMA, marketing authorization application; NDA, new drug application; QD, once per day; XR, extended release.
Winthrop, KL. *Nat Rev Rheumatol.* 2017;13(4):234-243; Genovese M, et al. *Arthritis Rheumatol.* 2016;68(12):2857-2866; Westhovens R. *Rheumatology (Oxford).* 2019;58(suppl 1):i27-i33.

TNT-002 Projected Sales for Rheumatoid Arthritis

Total Market Size for Oral RA Drugs	~\$9000 MM
JAK Inhibitors for RA Market Size	~\$3000MM

TNT-002

Market Penetration for TNT-002

10%

Initial Market Size for TNT-002

~\$300 MM

TNT-013 is a Risky Bet for Asthma

Phase I

Phase II



TNT Bio: **TNT-013**

Mechanism of Action:
IL-13 Inhibition (Injection)

Phase III



Leo Pharma: **Tralokinumab**

Comparable Mechanism of Action:
IL-13 Inhibition (Injection)



Dermira: **Lebrikizumab**

Comparable Mechanism of Action:
IL-13 Inhibition (Injection)

In The Market



FDA Approved for Asthma:
October 2018 (Adults)

Comparable Mechanism of Action: Blocks IL-4 and IL-13 via IL-4R α inhibition

Strong Sales: Revenues of over \$2.2 B in 2019, with projected growth up to \$10 B

TNT-013 is a Risky Bet for Asthma

Phase I

Phase II



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TNT-013 is a Risky Bet for Asthma

There is high risk of failure for **TNT-013** in Phase 3 trials for Asthma.

Factors	TNT-002	TNT-013
Co-indications		

TNT-002 Has Greater Opportunity for AD Treatment

Factors	TNT-002	TNT-013
Market Size	✓	
Ease of Manufacturing	✓	
Low Risk for Off-target Effects		✓
Competitive Landscape	✓	
Financial Justification	✓	
Co-indications	✓	
Regulatory Environment		
OVERALL CHOICE		

TNT-002 is Favored By Trends in The Payor Market

The payor market is trending towards:

- 1** | Manage utilization and control drug cost
- 2** | Employ formularies to control costs and control formulary placement.
- 3** | Implement “Copay Accumulators” that will shift the cost burden to manufacturers and consumers.
- 4** | Develop cost-containment strategies with specialty pharmaceuticals

The market is moving towards transparently priced, affordable drugs

Entitlement Reform

Medicare

Proposed budget would include **cuts totaling \$4.8T** to programs like Medicare over the next decade

Price Control & Transparency



States are beginning to implement **price transparency** and **price control** for drugs

Consumer Behavior



Consumers want **effective, safe, and affordable** treatments

Legal Reformatory Acts





Legal and consumer landscapes are shifting away from high cost pharmaceuticals towards more **transparently priced, affordable options**.

These changes further support the selection of **TNT-002**.

Factors	TNT-002	TNT-013
Regulatory Environment		

TNT-002 Has Greater Opportunity for AD Treatment







-  TNT Bio's Options
-  Product Comparison
-  **Solution**
-  Future Considerations

TNT-002 Has Greater Opportunity for AD Treatment

Factors	TNT-002	TNT-013
Market Size	✓	
Ease of Manufacturing	✓	
Low Risk for Off-target Effects		✓
Competitive Landscape	✓	
Financial Justification	✓	
Co-indications	✓	
Regulatory Environment	✓	
OVERALL CHOICE	✓✓✓✓✓✓	✓

TNT-002 Has Greater Opportunity for AD Treatment



-  TNT Bio's Options
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Future Considerations for TNT Bio



Consumer Landscape

- Application of TNT-002 for other co-indications such as:
 - Ulcerative colitis
 - Myelofibrosis
 - Psoriasis
 - Irritable Bowel Syndrome



Competitive Landscape

- New and existing competing therapeutics with similar targets
- Larger pharma companies with the upper hand in market penetration



Regulatory Landscape

- Changing regulations supporting reduced pricing and price transparency
- Regulation changes for payor market for specialty drugs

TNT Bio's Impact

Goals

Finding a market need

Maximizing profits within 15 years

Leveraging profitable co-indications

Findings

Develop TNT-002 to meet market need for moderate-severe AD patient segment

Develop TNT-002 to maximize profit growth in AD and RA

Continue development of TNT-002 for RA due to proven efficacy of similar therapeutics

Recommendation

We recommend that TNT Bio pursue **TNT-002** for development and sales for atopic dermatitis

Thank You For Listening!

For Questions, Please Feel Free to Reach Us Virtually



| [Andrew Chan](#) |



| [Ana Peredo](#) |



| [Eric Dai](#) |

APPENDIX

Findings

[AD Market Sizing](#)
[Market Sizing Data 1/6](#)
[Market Sizing Data 2/6](#)
[Market Sizing Data 3/6](#)
[Market Sizing Data 4/6](#)
[Market Sizing Data 5/6](#)
[Market Sizing Data 6/6](#)
[Market Sizing for RA Coincidence](#)

Financial Analysis

[Financial Pro-Forma TNT-002 \(1/6\)](#)
[Financial Pro-Forma TNT-002 \(2/5\)](#)
[Financial Pro-Forma TNT-002 \(3/5\)](#)
[Financial Pro-Forma TNT-002 \(4/5\)](#)
[Financial Pro-Forma TNT-002 \(5/5\)](#)
[Financial Pro-Forma TNT-013 \(1/5\)](#)
[Financial Pro-Forma TNT-013 \(2/5\)](#)
[Financial Pro-Forma TNT-013 \(3/5\)](#)
[Financial Pro-Forma TNT-013 \(4/5\)](#)
[Financial Pro-Forma TNT-013 \(5/5\)](#)
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Market Sizing

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AD Market Sizing

333M TOTAL U.S. POPULATION

~75M CHILDREN (<18 Years Old)



~258M ADULTS (>18 Years Old)

~13% Will Be Impacted By AD

~7% Will Be Impacted By AD

9.73 MM Children Impacted By AD

18.82 MM Adults Impacted By AD

TOTAL IMPACTED ~28.55 MM

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Market Sizing Data 1/6

Atopic Dermatitis																										
YEAR	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	
Part I: Finding What is The Population																										
US Population Projection	333	335	337	340	342	344	346	349	351	353	355	355	355	355	355	355	355	355	355	355	355	355	355	355	355	355
Human Population (Growth Rate)	0.72%	0.71%	0.70%	0.69%	0.68%	0.66%	0.65%	0.64%	0.62%	0.61%	0.59%	0.59%	0.59%	0.59%	0.59%	0.59%	0.59%	0.59%	0.59%	0.59%	0.59%	0.59%	0.59%	0.59%	0.59%	0.59%
Segmentation Data: Total Population of Each Age Segment																										
Children	75	75	75	75	75	75	75	75	75	75	75	75	75	75	75	75	75	75	75	75	75	75	75	75	75	76
Adults (>18 Years Old)	258	260	262	265	267	269	271	274	276	278	280	280	280	280	280	280	280	280	280	280	280	280	280	280	280	280
Total	333	335	337	340	342	344	346	349	351	353	355	355	355	355	355	355	355	355	355	355	355	355	355	355	355	356
Part II: Finding What is The Population Expected to Have AD																										
YEAR	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2030	2030	2030	2030	2030	2030	2030	2030	2030	2030	2030	2030	2030	2030	2030
Total Human Population Expected	333	335	337	340	342	344	346	349	351	353	355	355	355	355	355	355	355	355	355	355	355	355	355	355	355	355
% of Getting AD Based on Age Group																										
Segmentation Data: % with AD																										
Children	13.00%	13.00%	13.03%	13.03%	13.03%	13.00%	13.00%	13.00%	13.00%	13.00%	13.00%	13.00%	13.00%	13.00%	13.00%	13.00%	13.00%	13.00%	13.00%	13.00%	13.00%	13.00%	13.00%	13.00%	13.00%	13.00%
Adults	7%	7%	7%	7%	7%	7%	7%	7%	7%	7%	7%	7%	7%	7%	7%	7%	7%	7%	7%	7%	7%	7%	7%	7%	7%	7%
AD Growth Rate																										
Children	0.20%																									
Adults	9.73	9.73	9.74	9.74	9.75	9.75	9.75	9.76	9.76	9.76	9.77	9.77	9.77	9.78	9.78	9.78	9.79	9.79	9.80	9.80	9.80	9.81	9.81	9.81	9.81	9.82
Adults	18.82	18.99	19.16	19.33	19.49	19.65	19.82	19.98	20.13	20.29	20.44	20.44	20.43	20.43	20.43	20.43	20.43	20.42	20.42	20.42	20.42	20.41	20.41	20.41	20.41	20.41
Part III: Finding TNY2's Market Size																										
Total Addressable Market																										
Total Addressable Market	28.55	28.72	28.90	29.07	29.24	29.40	29.57	29.73	29.89	30.05	30.21	30.21	30.21	30.21	30.21	30.21	30.21	30.22	30.22	30.22	30.22	30.22	30.22	30.22	30.22	30.22
Market Penetration of Active Treatments for Atopic Dermatitis in the Market																										
Topical Emollients	25%	24%	24%	23%	22%	21%	21%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%	20%
Topical Corticosteroids	30%	28%	26%	24%	21%	19%	17%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%	15%
Topical Calcineurin Inhibitors	10%	9%	9%	8%	7%	6%	6%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%
Topical Immunomodulators	25%	28%	32%	38%	39%	43%	46%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%	50%
Systemic Immunomodulators	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%
Total %	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
Total Addressable Market																										
Topical Immunomodulator Market Size	7.14	8.21	9.29	10.38	11.49	12.60	13.73	14.87	14.95	15.03	15.10	15.10	15.10	15.10	15.11	15.11	15.11	15.11	15.11	15.11	15.11	15.11	15.11	15.11	15.11	15.11
Systemic Immunomodulators	2.85	2.87	2.89	2.91	2.92	2.94	2.96	2.97	2.99	3.01	3.02	3.02	3.02	3.02	3.02	3.02	3.02	3.02	3.02	3.02	3.02	3.02	3.02	3.02	3.02	3.02
Total Market Size (TMM)	9.99	11.08	12.18	13.29	14.41	15.54	16.69	17.84	17.94	18.03	18.12	18.12	18.12	18.12	18.13	18.13	18.13	18.13	18.13	18.13	18.13	18.13	18.13	18.13	18.13	18.13
Market Penetration vs Addressable Market Sensitivity Analysis (MM)																										
Market Size (MM)	7.14	8.21	9.29	10.38	11.49	12.60	13.73	14.87	14.95	15.03	15.10	15.10	15.10	15.10	15.11	15.11	15.11	15.11	15.11	15.11	15.11	15.11	15.11	15.11	15.11	15.11
1%	0.07	0.08	0.09	0.10	0.11	0.13	0.14	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15
5%	0.36	0.41	0.46	0.52	0.57	0.63	0.69	0.74	0.75	0.76	0.76	0.76	0.76	0.76	0.76	0.76	0.76	0.76	0.76	0.76	0.76	0.76	0.76	0.76	0.76	0.76
10%	0.71	0.82	0.93	1.04	1.15	1.26	1.37	1.49	1.49	1.50	1.51	1.51	1.51	1.51	1.51	1.51	1.51	1.51	1.51	1.51	1.51	1.51	1.51	1.51	1.51	1.51
15%	1.07	1.23	1.39	1.56	1.72	1.89	2.08	2.23	2.24	2.25	2.27	2.27	2.27	2.27	2.27	2.27	2.27	2.27	2.27	2.27	2.27	2.27	2.27	2.27	2.27	2.27
15 year projection starts (TMM, 10% Penetration Rate, Topical Immunomodulator)																										
	10.41																									
Market Penetration vs Addressable Market Sensitivity Analysis (Systemic)																										
Market Size (MM)	2.85	2.87	2.89	2.91	2.92	2.94	2.96	2.97	2.99	3.01	3.02	3.02	3.02	3.02	3.02	3.02	3.02	3.02	3.02	3.02	3.02	3.02	3.02	3.02	3.02	3.02
1%	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
5%	0.14	0.14	0.14	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15
10%	0.29	0.29	0.29	0.29	0.29	0.29	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30
15%	0.43	0.43	0.43	0.44	0.44	0.44	0.44	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45
15 year projection starts (TMM, 10% Penetration Rate, Systemic)																										
	2.31																									

Market Sizing Data 2/6 (Finding the Target Population)

Atopic Dermatitis												
YEAR	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031
Part I: Finding What is The Population												
US Population Projection	333	335	337	340	342	344	346	349	351	353	355	355
Human Population (Growth Rate)	0.72%	0.71%	0.70%	0.69%	0.68%	0.66%	0.65%	0.64%	0.62%	0.61%	0.59%	0.59%
<u>Segmentation Data, Total Population of Each Age Segment</u>												
Children	75	75	75	75	75	75	75	75	75	75	75	75
Adults (>18 Years Old)	258	260	262	265	267	269	271	274	276	278	280	280
Total	333	335	337	340	342	344	346	349	351	353	355	355

Atopic Dermatitis						
YEAR	2032	2033	2034	2035	2036	2037
US Population Projection	355	355	355	355	355	355
Human Population (Growth Rate)	0.59%	0.59%	0.59%	0.59%	0.59%	0.59%
<u>Segmentation Data, Total Population of Each Age Segment</u>						
Children	75	75	75	75	75	75
Adults (>18 Years Old)	280	280	280	280	280	280
Total	355	355	355	355	355	355

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Market Sizing Data 3/6 (Finding the Target Population)

YEAR	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029
Total Human Population Expected	333	335	337	340	342	344	346	349	351	353
% of Getting AD Based on Age Group										
<u>Segmentation Data, % with AD</u>										
Children	13.00%	13.00%	13.03%	13.03%	13.03%	13.00%	13.00%	13.00%	13.00%	13.00%
Adults	7%	7%	7%	7%	7%	7%	7%	7%	7%	7%
AD Growth Rate	0.20%									
<u>Segmentation Population, MM with AD</u>										
Children	9.73	9.73	9.74	9.74	9.75	9.75	9.75	9.76	9.76	9.76
Adults	18.82	18.99	19.16	19.33	19.49	19.65	19.82	19.98	20.13	20.29

YEAR	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044
Total Human Population Expected	355	355	355	355	355	355	355	355	355	355	355	355	355	355	355
% of Getting AD Based on Age Group															
<u>Segmentation Data, % with AD</u>															
Children	13.00%	13.00%	13.00%	13.00%	13.00%	13.00%	13.00%	13.00%	13.00%	13.00%	13.00%	13.00%	13.00%	13.00%	13.00%
Adults	7%	7%	7%	7%	7%	7%	7%	7%	7%	7%	7%	7%	7%	7%	7%
AD Growth Rate															
<u>Segmentation Population, MM with AD</u>															
Children	9.77	9.77	9.77	9.78	9.78	9.78	9.79	9.79	9.80	9.80	9.80	9.81	9.81	9.81	9.82
Adults	20.44	20.44	20.43	20.43	20.43	20.43	20.43	20.42	20.42	20.42	20.42	20.42	20.41	20.41	20.41

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Market Sizing Data 4/6 (Market Segmentation Based on Different Treatments)

		Part III: Finding TNT TYK2's Market Size					
Total Addressable Market	28.55	28.72	28.90	29.07	29.24	29.40	29.57
Market Penetration of Active Treatments for Atopic Dermatitis in the Market							
Topical Emollients	25%	24%	24%	23%	22%	21%	21%
Topical Corticosteroids	30%	28%	26%	24%	21%	19%	17%
Topical Calcineurin Inhibitors	10%	9%	9%	8%	7%	6%	6%
Topical Immunomodulators	25%	29%	32%	36%	39%	43%	46%
Systemic Immunomodulators	10%	10%	10%	10%	10%	10%	10%
Total %	100%	100%	100%	100%	100%	100%	100%

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Market Sizing Data 5/6 (Systemic Immunomodulators Market Size)

Market Penetration vs Addressable Market Sensitivity Analysis (Systemic)		2020	2021	2022	2023	2024	2025	2026	2027	2028
Market Size (MM)		2.85	2.87	2.89	2.91	2.92	2.94	2.96	2.97	2.99
1%		0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
5%		0.14	0.14	0.14	0.15	0.15	0.15	0.15	0.15	0.15
10%		0.29	0.29	0.29	0.29	0.29	0.29	0.30	0.30	0.30
15%		0.43	0.43	0.43	0.44	0.44	0.44	0.44	0.45	0.45

2029	2030	2031	2032	2033	2034	2035	2036	2037
3.01	3.02	3.02	3.02	3.02	3.02	3.02	3.02	3.02
0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15
0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30
0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45	0.45

15 year projection patients (MM), 10% Penetration Rate, Systemic

2.37

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Market Sizing Data 6/6 (Topical Immunomodulators Market Size)

Market Penetration vs Addressable Market Sensitivity Analysis (IM)		2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
Market Size (MM)		7.14	8.21	9.29	10.38	11.49	12.60	13.73	14.87	14.95	15.03	15.10
1%		0.07	0.08	0.09	0.10	0.11	0.13	0.14	0.15	0.15	0.15	0.15
5%		0.36	0.41	0.46	0.52	0.57	0.63	0.69	0.74	0.75	0.75	0.76
10%		0.71	0.82	0.93	1.04	1.15	1.26	1.37	1.49	1.49	1.50	1.51
15%		1.07	1.23	1.39	1.56	1.72	1.89	2.06	2.23	2.24	2.25	2.27
15 year projection patients (MM), 10% Penetration Rate, Topical Immunomodul		10.41										

2031	2032	2033	2034	2035	2036	2037
15.10	15.10	15.10	15.11	15.11	15.11	15.11
0.15	0.15	0.15	0.15	0.15	0.15	0.15
0.76	0.76	0.76	0.76	0.76	0.76	0.76
1.51	1.51	1.51	1.51	1.51	1.51	1.51
2.27	2.27	2.27	2.27	2.27	2.27	2.27

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Market Sizing Coindication - Rheumatoid Arthritis

Comparable Product:			
			Source
Total Market Size for Oral Auto-Immune Disorder Drugs	9000	MM by 2027	Figure 7
JAK Inhibitor Market	3000	MM by 2027	Figure 11
TNT 002 Market Penetration	10%	by 2027	Assumption
TNT 002 Market Revenue in 2007, at 20% Penetration Rate	300	MM by 2027	

Source: <https://www.belegger.nl/Forum/Upload/2018/10987448.pdf>

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Financial Analysis

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Financial Pro-Forma TNT-002 (1/5)

TNT 002								Starting Selling								
Revenue	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035
Price of TNT-013 (thousands)	0	0	0	0	0	0	10.00	10.30	10.61	10.93	11.26	11.59	11.94	12.30	12.67	13.05
Units Sold (thousands)	0	0	0	0	0	0	47	99	149	150	151	151	151	151	151	151
Revenue for TNT 002 in MM	0	0	0	0	0	0	467	1023	1581	1639	1700	1751	1803	1857	1913	1970.208
Net Income	0.000				0.000	0.000	466.667	1023.133	1580.741	1639.091	1699.518	1750.504	1803.019	1857.110	1912.823	1970.208
Cost Drivers							1570.281									
Research & development expense in MM	-333.333	-333.333	-333.333	-333.333	-333.333	-333.333	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Capital Goods and Equipment in MM	-500.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000
Cost of Goods Sold	0.000	0.000	0.000	0.000	0.000	0.000	-140.000	-306.940	-474.222	-491.727	-509.855	-525.151	-540.906	-557.133	-573.847	-591.062
Selling & marketing expense	0.000	0.000	0.000	0.000	0.000	-140.000	-140.000	-306.940	-474.222	-491.727	-509.855	-525.151	-540.906	-557.133	-573.847	-591.062
Total costs & expenses	-833.333	-383.333	-383.333	-383.333	-383.333	-523.333	-330.000	-663.880	-998.445	-1033.454	-1069.711	-1100.302	-1131.811	-1164.266	-1197.694	-1232.125
EBITDA	-833.333	-383.333	-383.333	-383.333	-383.333	-523.333	136.667	359.253	582.296	605.636	629.807	650.202	671.208	692.844	715.129	738.083
Year	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Net Income	-833.333	-383.333	-383.333	-383.333	-383.333	-523.333	136.667	359.253	582.296	605.636	629.807	650.202	671.208	692.844	715.129	738.083
PV	-799.401	-720.475	-1058.863	-1383.471	-1694.862	-2721.660	812.913	2394.502	4281.683	4852.943	5445.294	6016.440	6601.791	7201.746	7816.719	8447.139
IRR	8.11%															
Discount Rate	4.24%															
Payback Period	4.608 Years															

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Financial Pro-Forma TNT-002 (2/5)

TNT 002	2020	2021	2022	2023	2024	2025	Starting Selling	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035
Revenue																	
Price of TNT-013 (thousands)	0	0	0	0	0	0	10.00	10.30	10.61	10.93	11.26	11.59	11.94	12.30	12.67	13.05	
Units Sold (thousands)	0	0	0	0	0	0	47	99	149	150	151	151	151	151	151	151	151
Revenue for TNT 002 in MM	0	0	0	0	0	0	467	1023	1581	1639	1700	1751	1803	1857	1913	1970.208	
Net Income	0.000				0.000	0.000	466.667	1023.133	1580.741	1639.091	1699.518	1750.504	1803.019	1857.110	1912.823	1970.208	

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Financial Pro-Forma TNT-002 (3/5)

		2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035
Cost Drivers							1570.281										
Research & development expense in MM	-333.333	-333.333	-333.333	-333.333	-333.333	-333.333	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Capital Goods and Equipment in MM	-500.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000
Cost of Goods Sold	0.000	0.000	0.000	0.000	0.000	0.000	-140.000	-306.940	-474.222	-491.727	-509.855	-525.151	-540.906	-557.133	-573.847	-591.062	-591.062
Selling & marketing expense	0.000	0.000	0.000	0.000	0.000	-140.000	-140.000	-306.940	-474.222	-491.727	-509.855	-525.151	-540.906	-557.133	-573.847	-591.062	-591.062
Total costs & expenses	-833.333	-383.333	-383.333	-383.333	-383.333	-523.333	-330.000	-663.880	-998.445	-1033.454	-1069.711	-1100.302	-1131.811	-1164.266	-1197.694	-1232.125	-1232.125
EBITDA	-833.333	-383.333	-383.333	-383.333	-383.333	-523.333	136.667	359.253	582.296	605.636	629.807	650.202	671.208	692.844	715.129	738.083	738.083

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Financial Pro-Forma TNT-002 (4/5)

Year	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Net Income	-833.333	-383.333	-383.333	-383.333	-383.333	-523.333	136.667	359.253	582.296	605.636	629.807	650.202	671.208	692.844	715.129	738.083
PV	-799.401	-720.475	-1058.863	-1383.471	-1694.862	-2721.660	812.913	2394.502	4281.683	4852.943	5445.294	6016.440	6601.791	7201.746	7816.719	8447.139

Financial Pro-Forma TNT-002 (5/5)

IRR	8.11%
Discount Rate	4.24%
Payback Period	4.608 Years

Notes/Assumptions	
With Inflation at 2%, Compounded YOY	
in MM	
2 Billion Dollars R&D, Small Molecules are on the lower end.	
30% COGS to Revenue	
30% SG&A to Revenue	

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Financial Pro-Forma TNT-013 (1/5)

TNT 013	2020	2021	2022	2023	2024	2025	Starting Selling 2026	2027	2028	2029	2030	2031	2032	2033	2034	2035
Revenue																
Price of TNT-013 (thousands)	0	0	0	0	0	0	37	38	39	40	42	43	44	46	47	48
Units Sold (thousands)	0	0	0	0	0	0	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00
Revenue for TNT 002 in Millions	0	0	0	0	0	0	555	572	589	606	625	643	663	683	703	724.149
Total Revenue	0.000	0.000	0.000	0.000	0.000	0.000	555.000	571.650	588.800	606.463	624.657	643.397	662.699	682.580	703.057	724.149
Cost Drivers																
Research & development expense in Millions	-500.000	-500.000	-500.000	-500.000	-500.000	-500.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Capital Goods and Equipment in \$ Million	-500.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000
Cost of Goods Sold	0.000	0.000	0.000	0.000	0.000	0.000	-194.250	-200.078	-206.080	-212.262	-218.630	-225.189	-231.945	-238.903	-246.070	-253.452
Selling & marketing expense	0.000	0.000	0.000	0.000	0.000	-33.300	-166.500	-171.495	-176.640	-181.939	-187.397	-193.019	-198.810	-204.774	-210.917	-217.245
Total costs & expenses	-1000.000	-550.000	-550.000	-550.000	-550.000	-583.300	-410.750	-421.573	-432.720	-444.201	-456.027	-468.208	-480.754	-493.677	-506.987	-520.697
Net Income (EBIT)	-1000.000	-550.000	-550.000	-550.000	-550.000	-583.300	144.250	150.078	156.080	162.262	168.630	175.189	181.945	188.903	196.070	203.452
Year	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Net Income	-1000.000	-550.000	-550.000	-550.000	-550.000	-583.300	144.250	150.078	156.080	162.262	168.630	175.189	181.945	188.903	196.070	203.452
PV	-959.281	-1033.725	-1519.238	-1984.980	-2431.758	-3033.524	858.019	1000.299	1147.670	1300.202	1457.970	1621.058	1789.552	1963.547	2143.144	2328.450
IRR	8.53%															
Discount Rate	4.24%															
Payback Period	24.240 Years															

Financial Pro-Forma TNT-013 (2/5)

	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035
Revenue																
Price of TNT-013 (thousands)	0	0	0	0	0	0	37	38	39	40	42	43	44	46	47	48
Units Sold (thousands)	0	0	0	0	0	0	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00	15.00
Revenue for TNT 002 in Millions	0	0	0	0	0	0	555	572	589	606	625	643	663	683	703	724.149

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Financial Pro-Forma TNT-013 (3/5)

	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035
Cost Drivers																
Research & development expense in Millions	-500.000	-500.000	-500.000	-500.000	-500.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Capital Goods and Equipment in \$ Million	-500.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000	-50.000
Cost of Goods Sold	0.000	0.000	0.000	0.000	0.000	0.000	-194.250	-200.078	-206.080	-212.262	-218.630	-225.189	-231.945	-238.903	-246.070	-253.452
Selling & marketing expense	0.000	0.000	0.000	0.000	0.000	-33.300	-166.500	-171.495	-176.640	-181.939	-187.397	-193.019	-198.810	-204.774	-210.917	-217.245
Total costs & expenses	-1000.000	-550.000	-550.000	-550.000	-550.000	-583.300	-410.750	-421.573	-432.720	-444.201	-456.027	-468.208	-480.754	-493.677	-506.987	-520.697
Net Income (EBIT)	-1000.000	-550.000	-550.000	-550.000	-550.000	-583.300	144.250	150.078	156.080	162.262	168.630	175.189	181.945	188.903	196.070	203.452

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Financial Pro-Forma TNT-013 (4/5)

Year	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Net Income	-1000.000	-550.000	-550.000	-550.000	-550.000	-583.300	144.250	150.078	156.080	162.262	168.630	175.189	181.945	188.903	196.070	203.452
PV	-959.281	-1033.725	-1519.238	-1984.980	-2431.758	-3033.524	858.019	1000.299	1147.670	1300.202	1457.970	1621.058	1789.552	1963.547	2143.144	2328.450

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Financial Pro-Forma TNT-013 (5/5)

IRR	8.53%
Discount Rate	4.24%
Payback Period	24.240 Years

Notes/Assumptions	
With Inflation at 2%, Compounded YOY	
in Millions	
Revenue Income Stream for first 5 Years of Drug Launch	
25% of Revenue to R&D	
10% of Revenue to CAPEX	
35% COGS to Revenue	
30% SG&A to Revenue	

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Discount Rate Analysis (2/2)

Step 5 Find Cost of Debt				
		Total Liability	Interest	Cost of Debt
Regeneron and Sanofi		737.5	30.2	4.09%
Pfizer		53470	1574	2.94%
Dermira (Eli Lilly)		353	15	4.25%
Average Cost of Debt				3.76%
WACC				
Cost of Equity	7%			
Average Equity Weights	0.43			
Cost of Debt	3.76%			
Average Debt Weights	0.57			
Tax Rate	37%			
WACC	4.24%	Discount Rate		

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Atopic Dermatitis (AD)

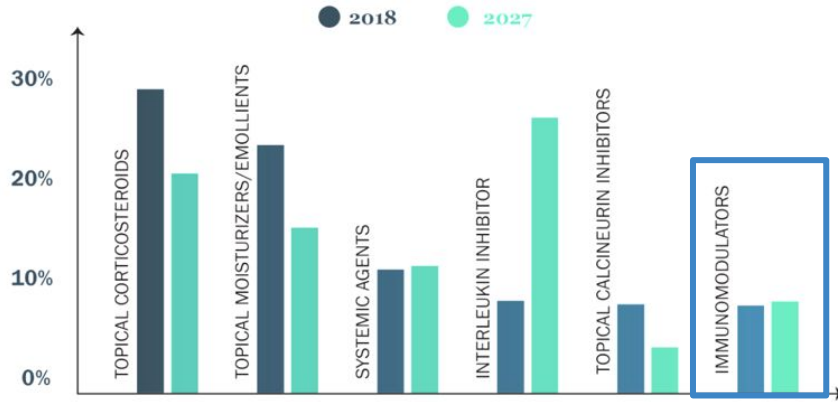
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AD Epidemiology

- Chronic inflammatory skin disease that results in itching and dry skin
 - Increase in inflammatory molecules
- **Patient population:**
 - 15-20% of children are affected (>285M)
 - 1-3% of adults are affected (>60M)
- **Patient segments:**
 - 60% <1 yr of age -> 207M
 - 30% 1-5 yrs. of age -> 103.5M
 - 10% >5 yrs of age -> 34.5M
- **Cost:**
 - >\$5B annually
 - \$3,302\$/year, \$4.463\$/yr for severe cases out-of-pocket expenses

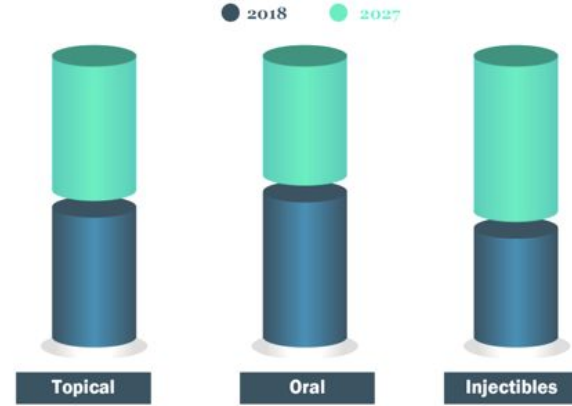
AD Market

Market by Drug Class



- **Global Market Size:** \$10.4B
 - **CAGR:** 8.2% (2017-2023)

Market by Route of Administration



Order of treatments prescribed:

1. Emollients/Moisturizers (25%)
2. Topical Corticosteroids (30%)
3. Topical Calcineurin Inhibitors (8%)
4. Topical Immunomodulators (25%)
5. Systemic Immunomodulators (12%)

AD Competitive Landscape

Major Players

- 1 Allergan PLC
- 2 BAUSCH HEALTH COMPANIES INC.
- 3 Novartis International AG
- 4 Pfizer Inc.
- 5 LEO PHARMA INC.

Major players in JAK-STAT Inhibitors:

1. Regeneron
2. Sanofi

In phase 3 clinical trials:

1. Pfizer
2. Eli Lilly
3. AbbVie
4. Leo Pharma
5. Asana Biosciences

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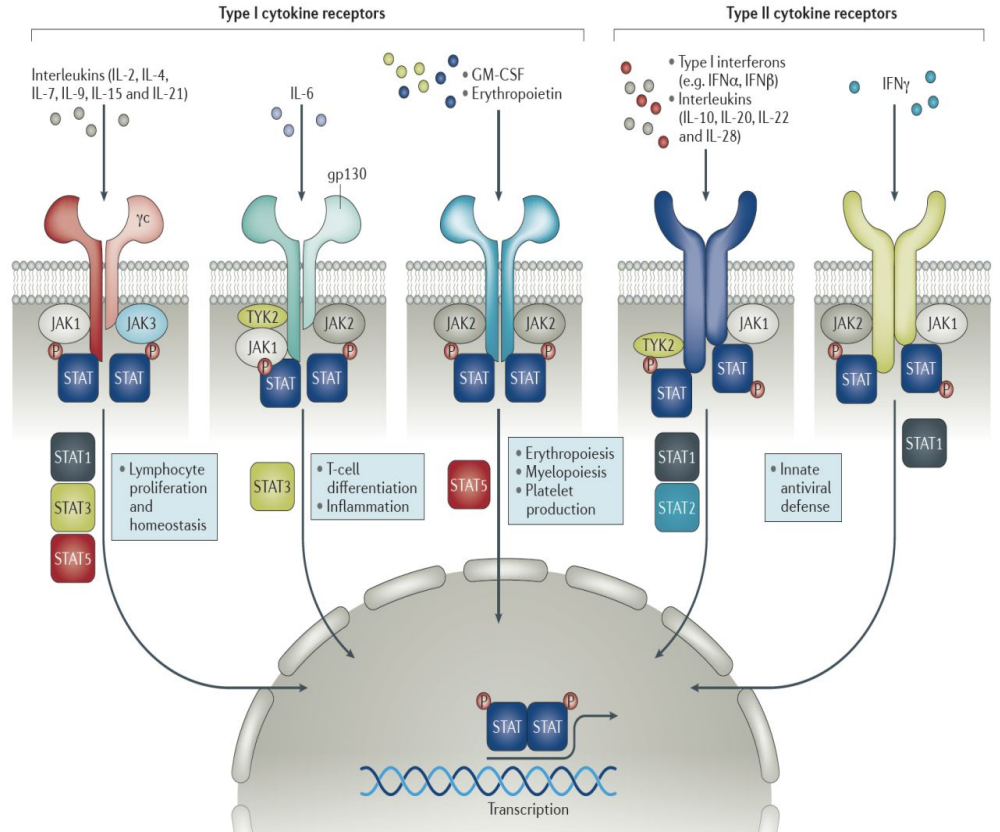
JANUS KINASES (JAKS)

- A subgroup of non-receptor protein tyrosine kinases^{1,2}
 - JAK1, JAK2, JAK3, and TYK2
- Characterised by two adjacent kinase domains (JH1 and JH2)³
- Implicated in cell growth, survival, development and cell differentiation¹
- Essential for immune and hematopoietic cells¹



JAK, Janus family kinase; TYK2, tyrosine kinase 2.

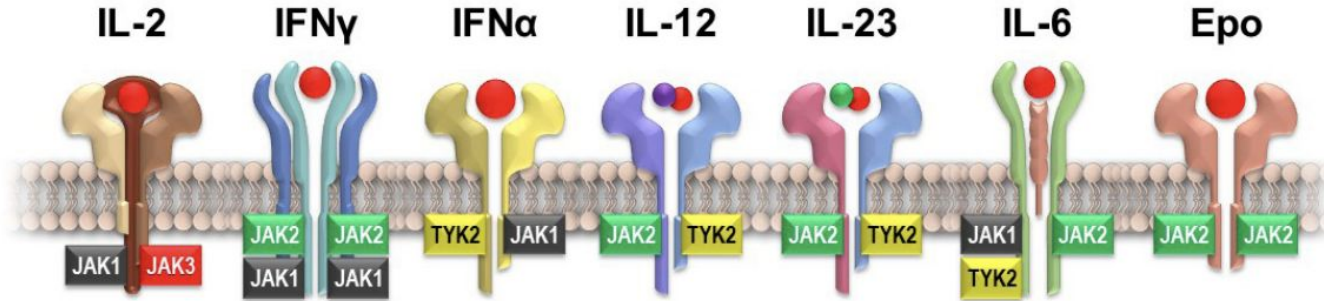
JAK-STAT INHIBITION AFFECTS MANY ASPECTS OF THE IMMUNE RESPONSE



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JAK-STAT INHIBITORS AFFECT DISTINCT CYTOKINES

JAK Inhibition on Signaling of Key Immunoregulatory Cytokines



Inhibitor	JAK1	JAK2	JAK3	TYK2	IL-2	IFN γ	IFN α	IL-12	IL-23	IL-6	Epo
JAK1	+	-	+	-	+	+	+	-	-	+	-
JAK2	-	+	-	+	-	+	+	+	+	+	+
JAK3	+	-	+	-	+	-	-	-	-	-	-
TYK2	-	-	-	+	-	-	+	+	+	-	-

Cytokine Signaling Partially Suppressed, Not Completely Blocked

Epo, erythropoietin.
O'Shea J, et al. *Immunity*. 2012;36(4):542-550.

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Selected Topical JAK Inhibitors in Development

Selected topical Jak inhibitors in development				
Project	Company	Indication(s)	Mechanism	Status
JTE-052/delgocitinib	Japan Tobacco, Torii Pharmaceutical	Atopic dermatitis	Jak inhibitor	Filed (Japan)
Topical ruxolitinib/ INCB018424	Incyte	Atopic dermatitis, vitiligo	Jak 1 & 2 inhibitor	Phase III
ATI-502	Aclaris Therapeutics	Atopic dermatitis, alopecia, vitiligo	Jak 1 & 3 inhibitor	Phase II
CTP-543	Concert Pharmaceuticals	Alopecia	Jak 1 & 2 inhibitor	Phase II
SNA-125	Sienna Biopharmaceuticals	Atopic dermatitis	Trk A & Jak 3 inhibitor	Phase II

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Antibody vs. Small Molecules

	Monoclonal Antibody Biological DMARDS	Targeted Synthetic DMARDS
Size:	~150.000 Da	~500 Da
Structure:	Immunoglobulin	Chemical entity
Production:	Made from cell culture media; very complex	Controlled chemical synthesis; not complex
Target:	Extracellular	Intracellular or extracellular
Target specificity:	High	Low(er)
Metabolism:	RES	Hepatic/renal
Administration:	Parenteral	Oral
Antidrug antibodies	Yes	No
Dosing:	~Q2W-Q4W	~QD
Cross blood-brain barrier:	No	Potentially
Price:	High	High

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Small Molecule vs mAb

Properties	Small Molecule Drugs	mAb Drugs
Size	Small, single molecule with low molecular weight	Large, complex with high molecular weight
Manufacturing process	Chemically synthesized, combining specific chemical ingredients in an ordered process	Produced in living cell cultures
Stability	Stable in all environments	Unstable, sensitive to external conditions
Production cost	Low cost	High cost
Target	Any drug-able target	Extracellular proteins
Side Effects	Less specific action; can inhibit multiple mechanisms	Specific action, low off-target toxicity

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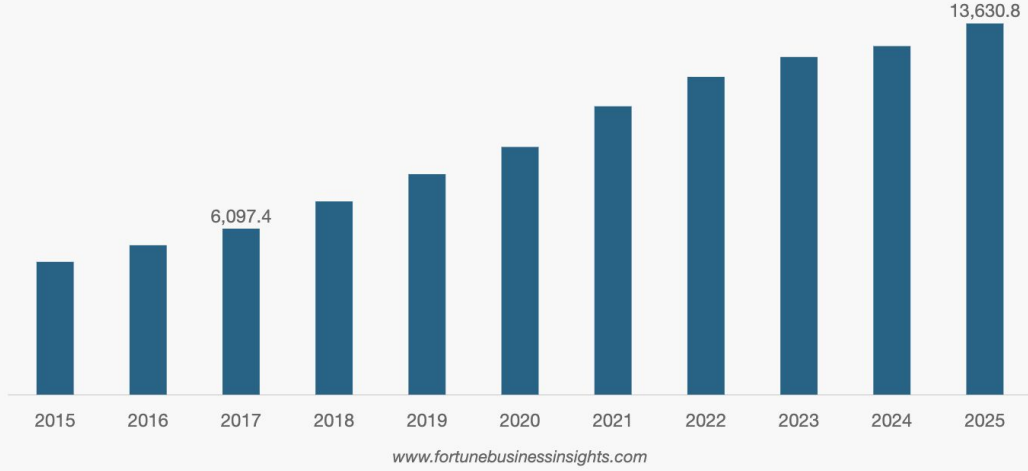
Global Eczema Therapeutic Market Size Shows TNT-002 a Promising Future

Table 6-5: The Worldwide Market for Prescription Dermatitis and Seborrhea Drugs by Type, 2016-2021

Year	Manufacturer Revenue (in millions)				Growth Rate
	Topical	Systemic	Others	Total	
2014	625.5	63.2	448.0	1,136.4	-
2015	631.0	63.5	455.0	1,149.5	1.2%
2016	638.0	64.5	466.0	1,168.5	1.7%
2017	647.0	65.6	482.0	1,194.6	2.2%
2018	658.0	66.9	500.0	1,224.9	2.5%
2019	675.0	68.4	520.0	1,263.4	3.1%
2020	695.0	70.2	542.5	1,307.7	3.5%
2021	718.0	72.1	580.0	1,370.1	4.8%
Years	Compound Annual Growth Rate				
	Topical	Systemic	Others	Total	
2014–2016	1.0%	1.0%	2.0%	1.4%	
2016–2021	2.4%	2.3%	4.5%	3.2%	
2014–2021	2.0%	1.9%	3.8%	2.7%	

Source: Kalorama Information

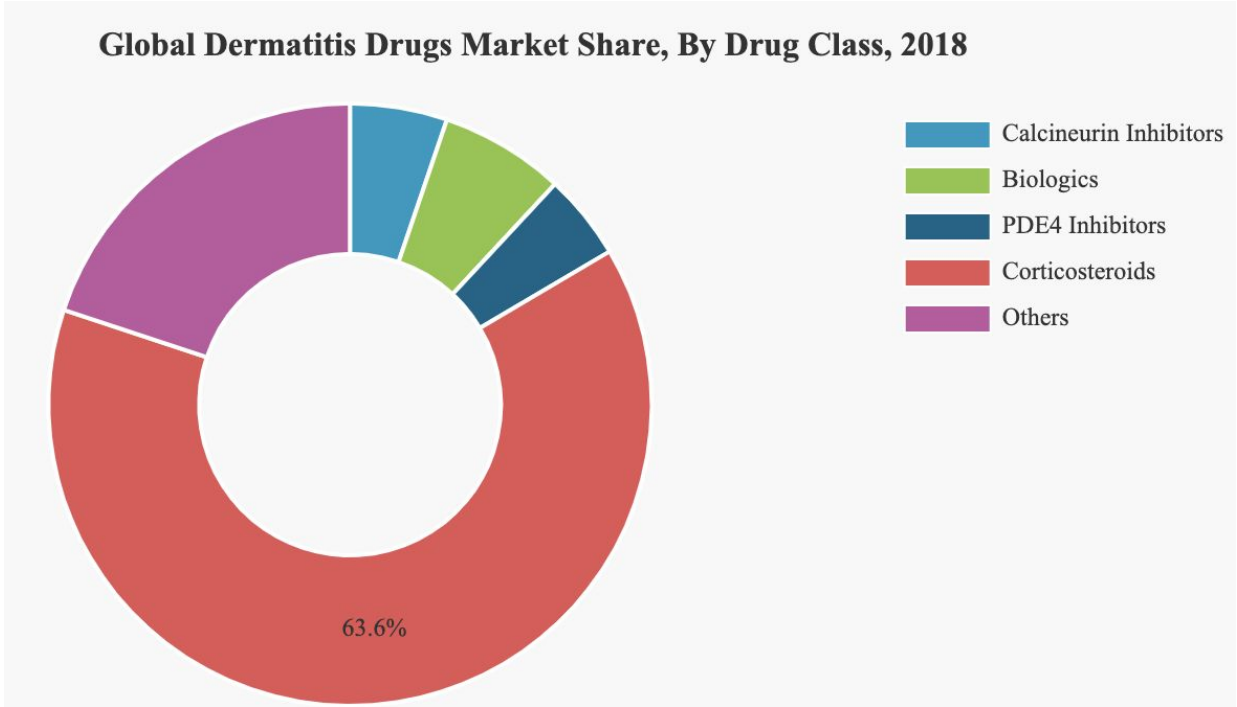
Global Dermatitis Drugs Market Size, 2015-2026 (USD Million)



- Market size:** Global Eczema Therapeutics market size is estimated to grow at CAGR of over 9% with Revenue USD 3.60 billion during the forecast period 2020-2024. The YOY (year-over-year) growth rate for 2020 is estimated at 7.09% by the end of 2024.

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Global Dermatitis Drugs Market Share



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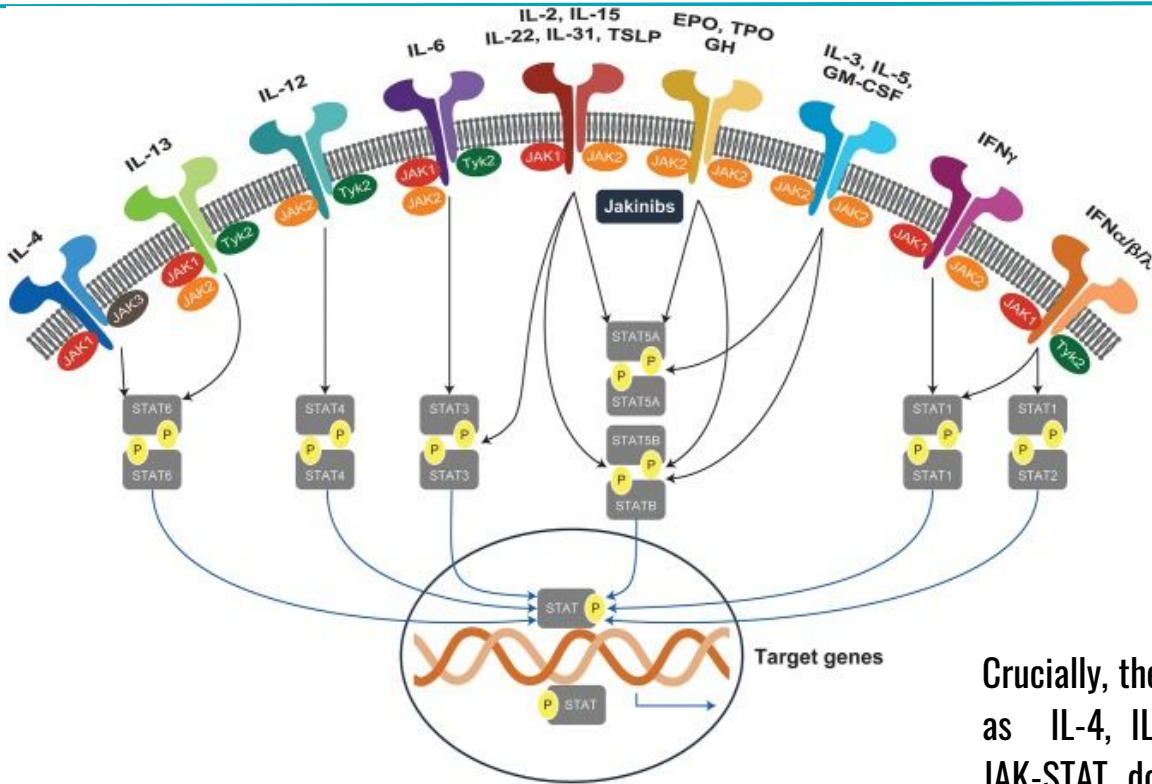
Global Market Leaders for Eczema Treatment

Competitive Landscape:

- Global market leaders for eczema treatment: ([Source](#))
 - AbbVie Inc.
 - Alliance Pharma Plc
 - Bausch Health Companies Inc.
 - Bayer AG
 - Eli Lilly and Co.
 - Encore Dermatology Inc.
 - LEO Pharma AS
 - Mylan NV
 - Pfizer Inc.
 - Sanofi

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TYK2 (Tyrosine Kinase 2) Inhibitor (Topical treatment) Diagram



Crucially, the cytokines involved in AD such as IL-4, IL-13, IL-31, and IL-22 require JAK-STAT downstream signaling for their biological function.

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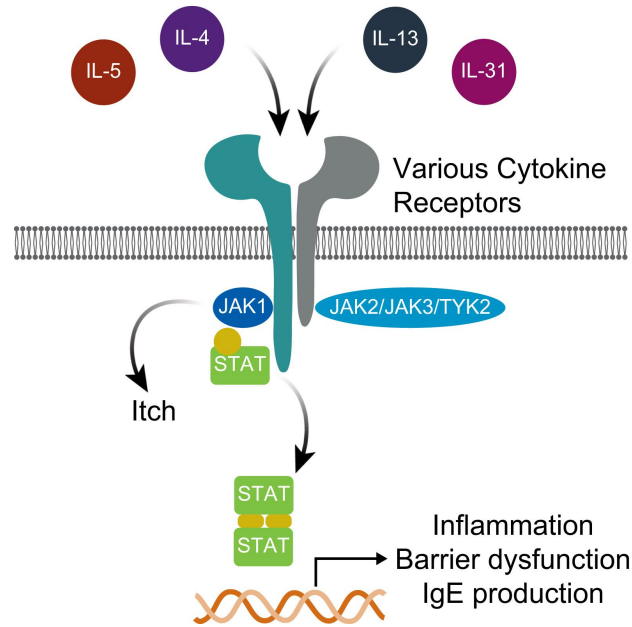
Molecules that target the JAK-STAT receptors (1/2)

- Oral:
 - Tofacitinib (JAK1/3) Sold by Pfizer for AD
 - Abrocitinib (JAK1) Sold by Pfizer for AD
 - Baricitinib (JAK1/2) Sold by Eli Lilly/Incyte for AD
 - Upadacitinib (JAK1) Sold by AbbVie for AD (Clinical trial ongoing)
 - ASN002 (JAK1/2/3, TYK2, SYK) Sold by Asana Biosciences for AD
- Topical:
 - Tofacitinib (JAK1//3) Sold by Pfizer for AD
 - PF-06700841 (JAK1/TYK2) Sold by Pfizer for AD (Clinical trial ongoing)
 - Ruxolitinib (JAK1/2) Sold by Incyte (Clinical Trial ongoing)
 - ATI-502 (JAK1/3) Sold by Aclaris
 - Delgocitinib (JAK1/2/3 Syk Tyk) Sold by Japan Tobacco Inc., Leo (Ongoing Clinical trial for AD)

Molecules that target the JAK-STAT receptors (2/2)

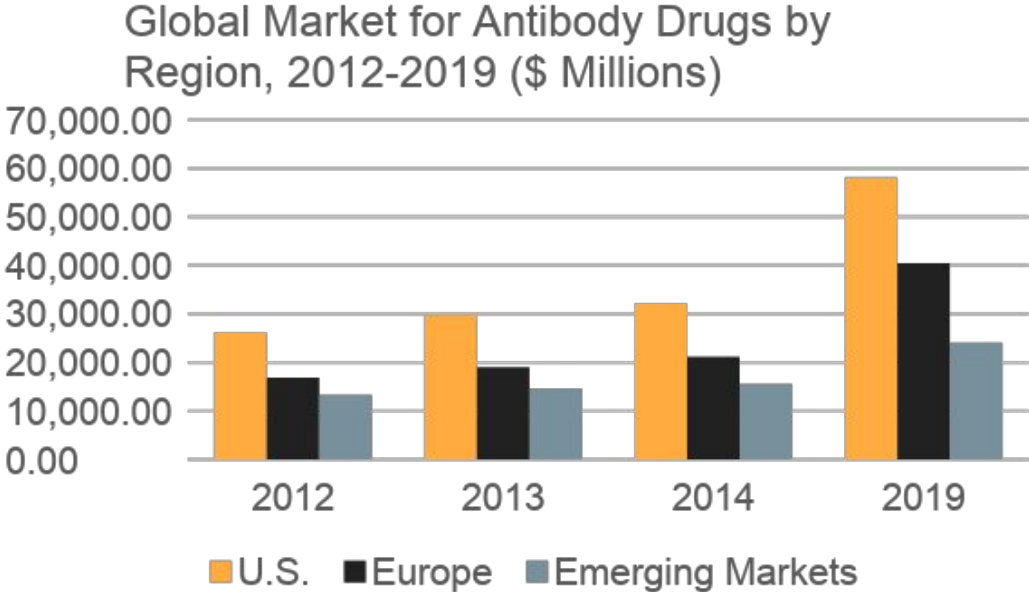
- [BMS-986165](#) (TYK2 inhibitor)
- Bristol Myers Squibb
 - **Phase III** Plaque psoriasis
 - **Phase II** Crohn's disease; Psoriatic arthritis; Systemic lupus erythematosus; Ulcerative colitis
 - **Phase I** Autoimmune disorders; Inflammatory bowel diseases; Liver disorders
- Similar efficacy to biologics without the effects on biomarkers associated with Janus kinase inhibitors. The selectivity against other Jak family subtypes (such as Jak2) is **crucial** in order to minimize the potential side effects and to maximize the desired pharmacological effects.

TYK2 for RA



- TYK2 is involved in the signaling cascade of IL-12, IL-23, type-I IFN as well as IL-6 and IL-10
- A specific TYK2 inhibitor would have less broad immunosuppression and, therefore, could be safely used for diseases such as psoriasis or inflammatory bowel disease for which inhibition of IL-12 and IL-23 is proving quite successful.

Global Market for Antibody Drugs by Region



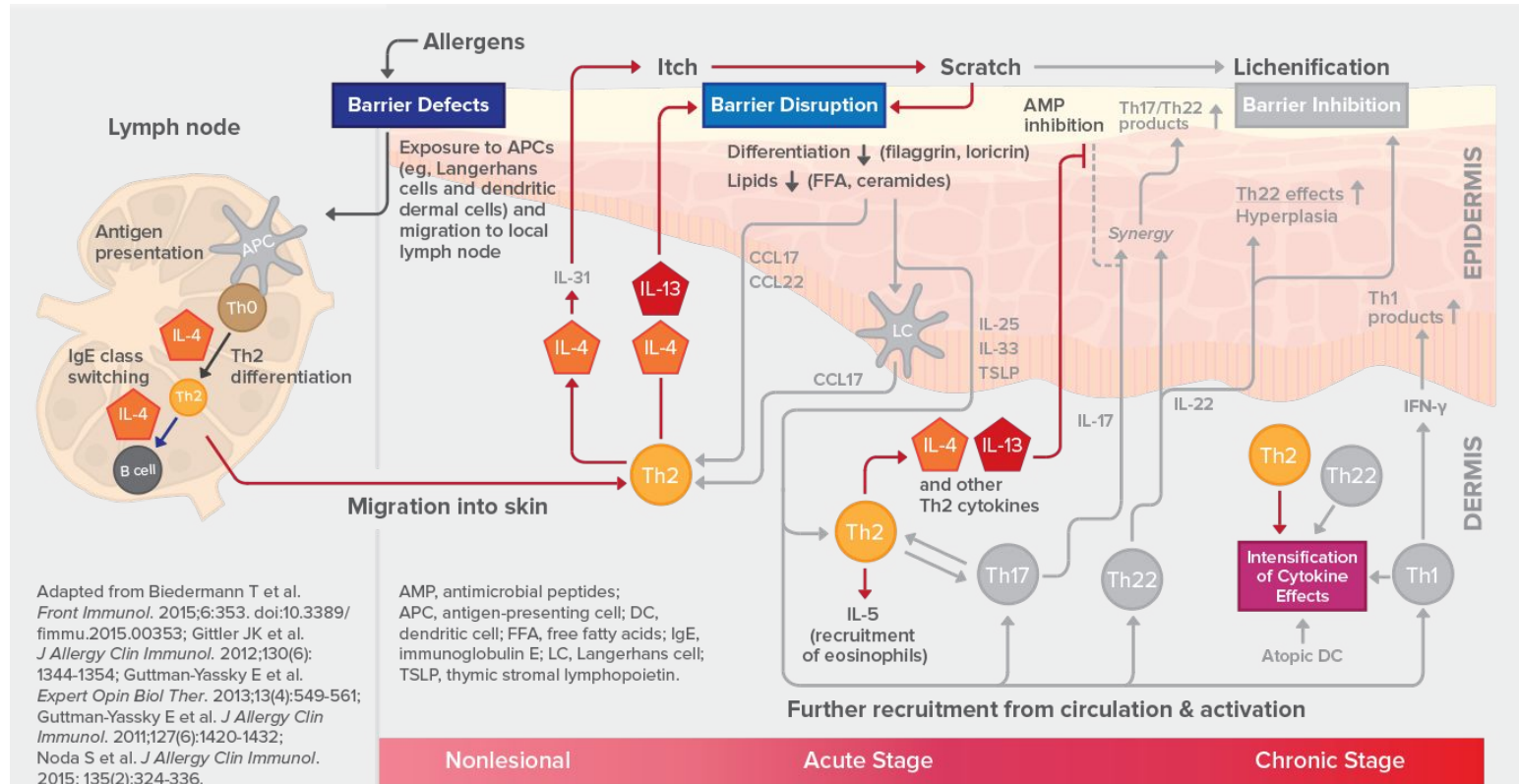
- Antibody drugs have grown at CAGR of 12.2% in the global market

Atopic Dermatitis Has a Large Patient Population With Unmet Needs

- Symptoms of AD include skin pruritis (itchiness), loss of skin barrier function, and increased skin infections
- Around 6.5 million American adults have severe AD, incurring an economic burden of ~\$5.37 Billion in 2016
- Treatments for severe AD include topical anti-inflammatory creams (i.e., topical corticosteroid and topical calcineurin inhibitors)
- Systemic agents are effective as a last line treatment, but have moderate to severe side effects, including immunosuppression



Atopic Dermatitis pathogenesis is driven by IL-4 and IL-13 Signaling

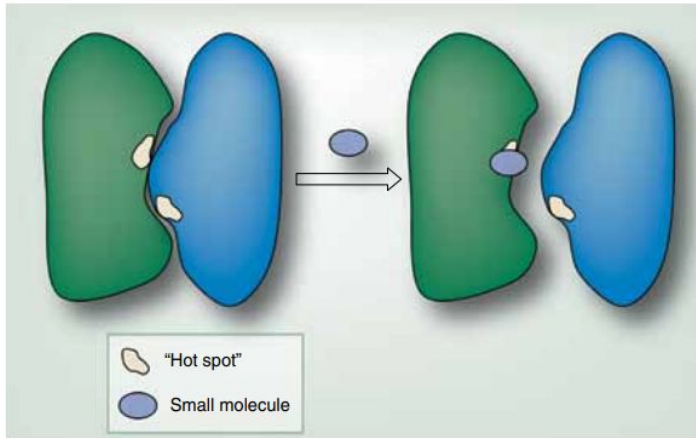


Adapted from Biedermann T et al. *Front Immunol.* 2015;6:353. doi:10.3389/fimmu.2015.00353; Gittler JK et al. *J Allergy Clin Immunol.* 2012;130(6):1344-1354; Guttman-Yassky E et al. *Expert Opin Biol Ther.* 2013;13(4):549-561; Guttman-Yassky E et al. *J Allergy Clin Immunol.* 2011;127(6):1420-1432; Noda S et al. *J Allergy Clin Immunol.* 2015; 135(2):324-336.

IL-4 and IL-13 represent key upstream drivers in the Th2 pathway that modulate multiple downstream mediators—including IL-5, IL-31, and IgE—setting in motion the chronic underlying inflammation of atopic dermatitis.^{1,5,10-12}

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mAb-Based Therapeutics Directly Target Pathogenic Protein Interactions

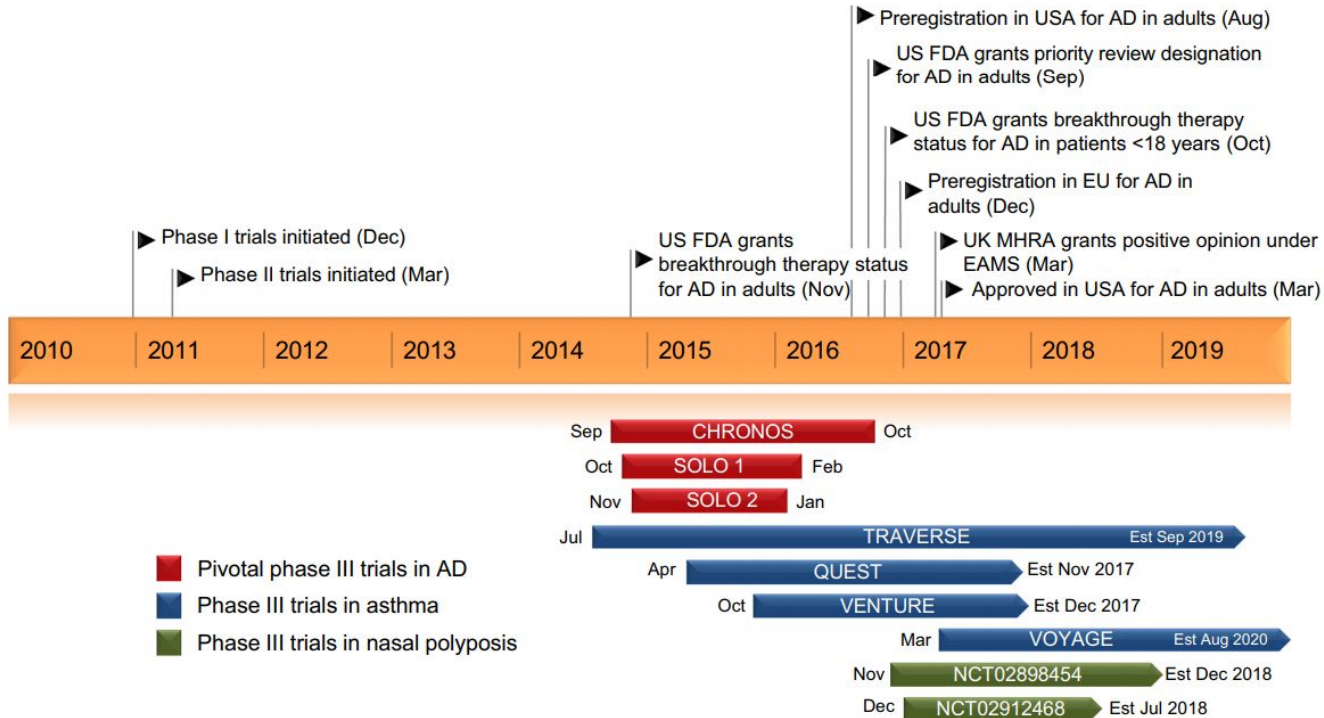


- Aberrant protein-protein interactions are central in disease pathogenesis
- Monoclonal antibodies bind a specific region of a protein to prevent pathogenic interactions

Selective inhibition of TYK2 can provide pharmacological benefits in the treatment of many diseases

- Psoriasis
- Systemic lupus erythematosus (SLE)
- Inflammatory bowel disease (IBD)
- Rheumatoid arthritis (RA)
- Cancer
- Diabetes

Reference Timeline for Dupilumab



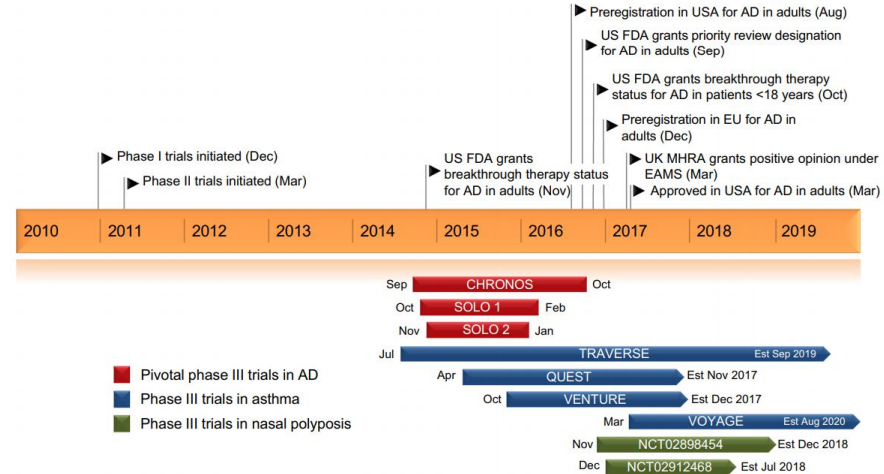
Clinical development of dupilumab. *AD* atopic dermatitis, *EAMS* Early Access to Medicines Scheme, *Est* estimated date of completion, *MHRA* Medicines and Healthcare Products Regulatory Agency

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TNT-013 has steep competition in AD



FDA Approved for AD: March 2017 (adults) and March 2019 (adolescents)

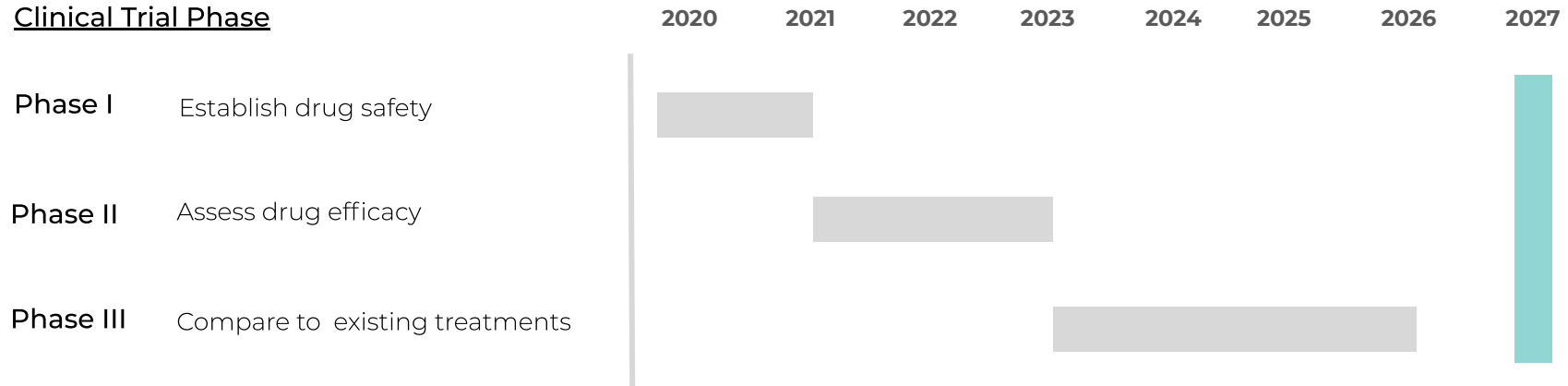


Clinical development of dupilumab. AD atopic dermatitis, EAMS Early Access to Medicines Scheme, Est estimated date of completion, MHRA Medicines and Healthcare Products Regulatory Agency



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TNT-002 and TNT-013 Have Similar Clinical Trial Timelines



* Assuming average clinical trial length for similar products in the market for each phase

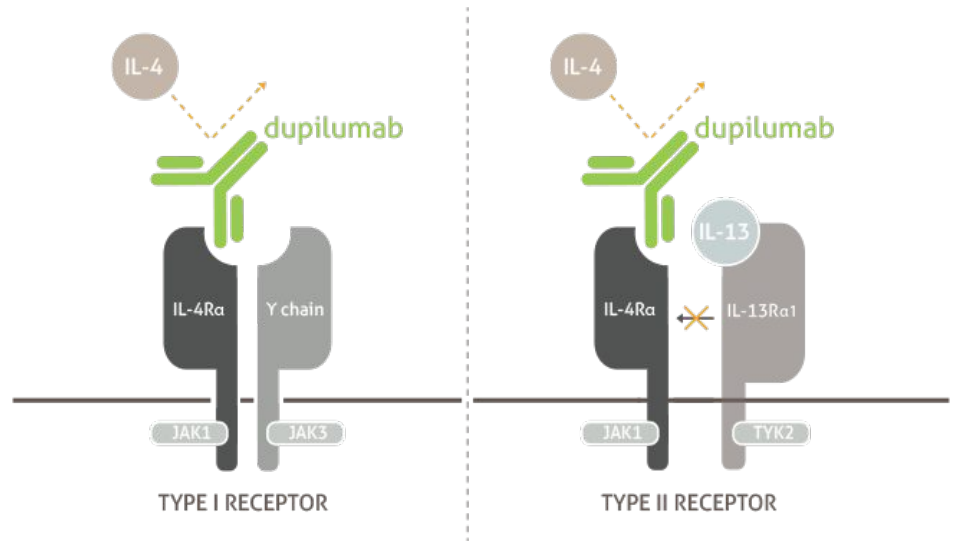
TNT-013 has steep competition in AD

SANOFI
REGENERON

DUPIXENT™
(dupilumab)

FDA Approved for AD: March 2017 (adults)
and March 2019 (adolescents)

Comparable Mechanism of Action: Blocks
IL-4 and IL-13 via IL-4R α inhibition



© 2019 Sanofi and Regeneron Pharmaceuticals, Inc

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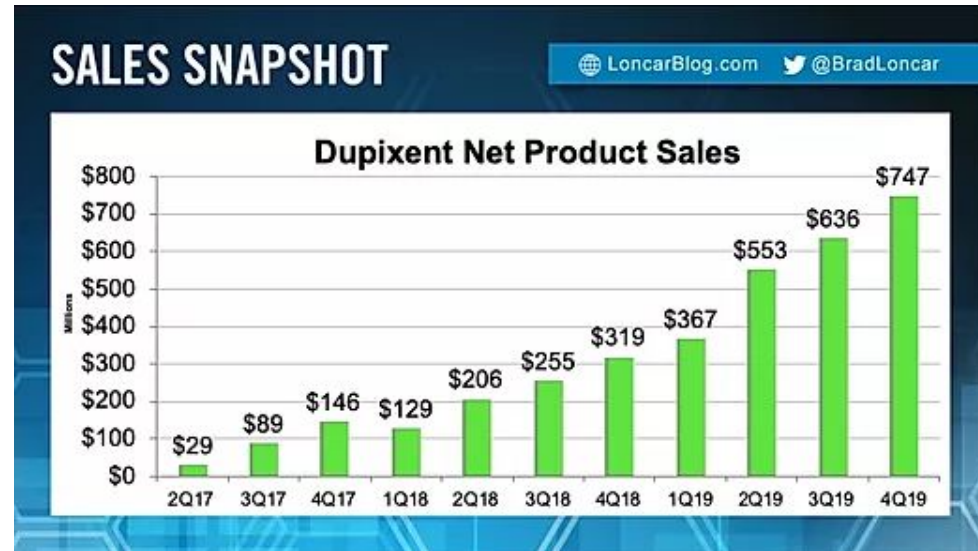
TNT-013 has steep competition in AD



- **FDA Approved for AD:** March 2017 (adults) and March 2019 (adolescents)

- **Comparable Mechanism of Action:** Blocks IL-4 and IL-13 via IL-4R α inhibition

- **Strong Sales:** Revenues of over \$2.2 B in 2019, with projected growth up to \$10 B



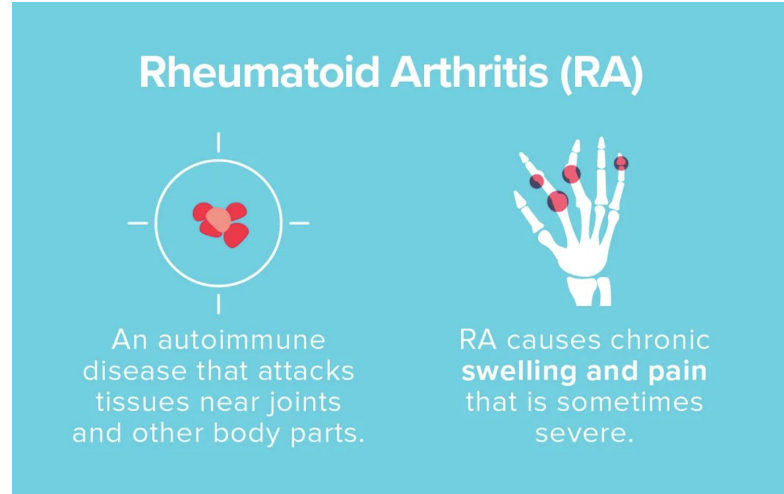
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Rheumatoid Arthritis (RA)

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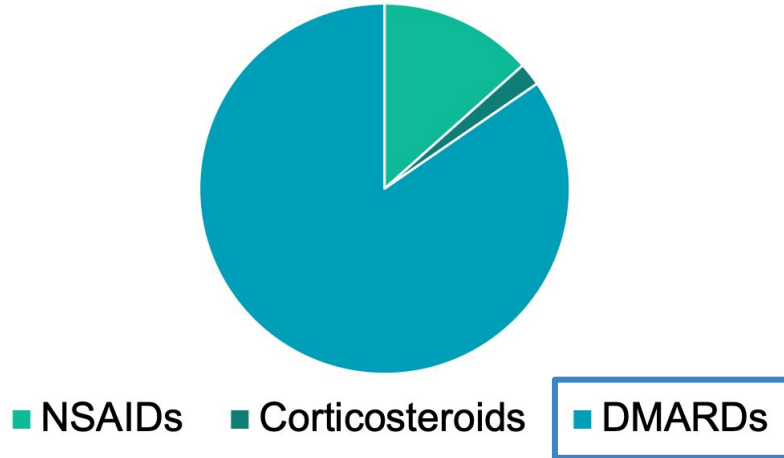
Rheumatoid Arthritis Epidemiology

- Chronic autoimmune disease that causes inflammation of the joints
 - Increase in inflammatory molecules
- **Patient population:**
 - 0.24-1% of the worldwide population (>78M)
- **Patient segments:**
 - Starts between ages of 30-60



Rheumatoid Arthritis Market

Global Small Molecule Therapies for RA
Market Share (2017)



- **Global Market Size:** \$2B
 - **CAGR:** 6.6% (2017-2022)

**Non-steroidal Anti-inflammatory
Drugs (NSAIDs)**

USD: 223.5M

Corticosteroids

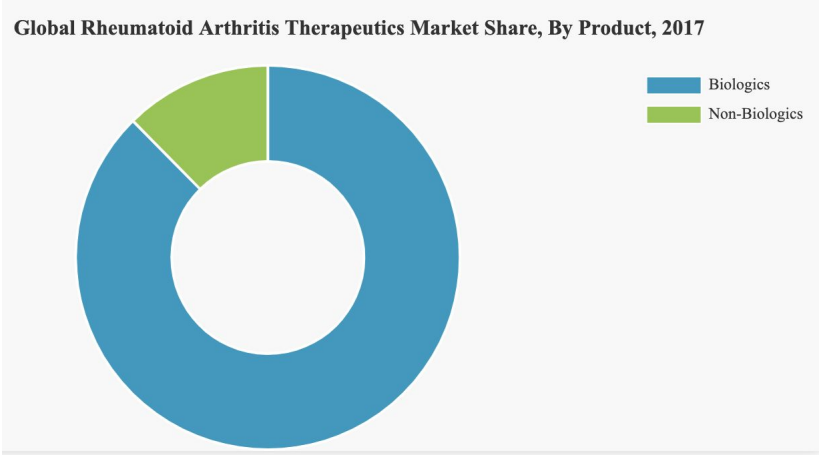
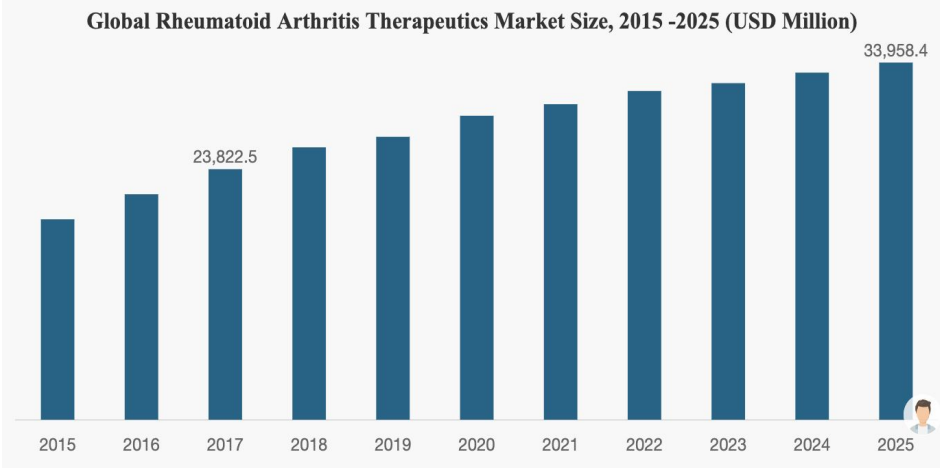
USD: 33.2M

**Disease-Modifying Anti-Rheumatic
Drugs (DMARDs)**

USD: 1,411M

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Rheumatoid Arthritis Size



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Rheumatoid Arthritis Cost of Care

RA annual
medication costs



\$15,000 - \$20,000*
per patient treated
with biologic agent

*year 2007 dollars

RA
costs



\$5,763*
per patient
per year

*year 2000 dollars

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Rheumatoid Arthritis Competitive Landscape

Global Market Shares for Key Competitors of Small Molecules Therapies for RA, 2017

Competitor	Market Share (%)	Revenue (\$ Millions)
AbbVie Inc.	30.9	525.0
F. Hoffmann-La Roche	15.8	269.4
Amgen Inc.	9.1	154.8
Pfizer	6.4	108.2
Bristol-Myers Squibb	4.2	70.6
Johnson & Johnson	3.1	52.2
UCB S.A.	2.6	44.9
Mitsubishi Tanabe Pharma Corporation	1.5	25.4
Biogen	0.6	10.8
Merck & Co.	0.6	10.3
Others	25.2	396.3

Major players in JAK-STAT Inhibitors:

1. Pfizer
2. Eli Lilly
3. AbbVie

In phase 3 clinical trials:

- Gilead Sciences, Inc.

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Rheumatoid Arthritis mAb Market, 2017-2022

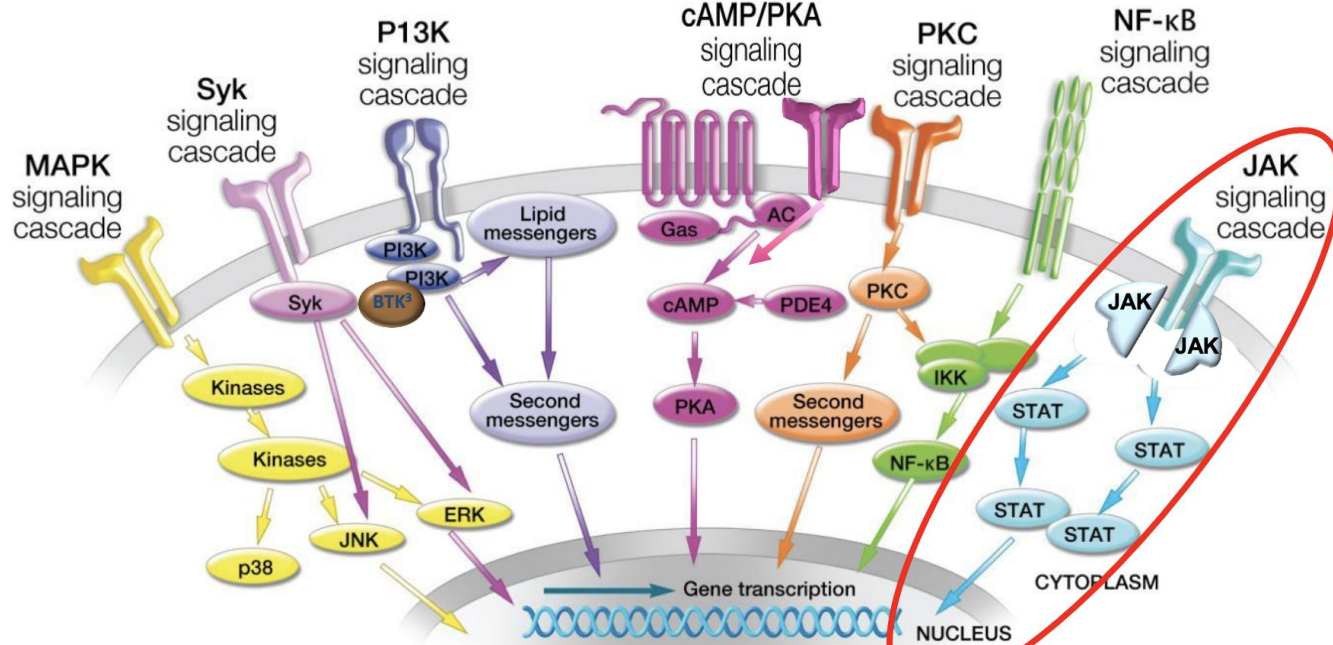
Table 5-2: Rheumatoid Arthritis mAb Market, 2017-2022 (\$ millions)

	2017 \$	2022 \$	GAGR 2017-2022
Rheumatoid Arthritis mAb Sales	\$ 23,492	\$ 24,660	1.0

Source: Kalorama Information

Cytokine Signaling Pathways in RA

Cytokines act via receptor binding



AC, adenylyl cyclase; BTK, Bruton tyrosine kinase; cAMP, cyclic adenosine monophosphate; ERK, extracellular-signal-regulated kinases; IKK, κB kinase; JAK, Janus kinase; JNK, c-Jun NH2-terminal kinase; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PDE4, phosphodiesterase 4; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; PKC, protein kinase C; STAT, signal transducer and activator of transcription; Syk, spleen tyrosine kinase.

1. Mavers M, et al. *Curr Rheum Rep* 2009;11:378–385.
2. Rommel C, et al. *Nat Rev Immunol* 2007;7:191–201.
3. Taskén K, et al. *Physiol Rev* 2004;84:137–167.
4. Baier G, et al. *Curr Opin Cell Biol* 2009;21:262–267.
5. O’Sullivan LA, et al. *Molec Immunol* 2007; 44:2497–2506.

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JAK Inhibitors on the Way for RA and Other Indications

JAK INHIBITORS ON THE WAY

Name:	JAK inhibition:	Disorders under investigation:
Filgotinib	JAK1	RA, AS, PsA, Sjogren, CD, UC, uveitis
Upadacitinib	JAK1	RA, AS, PsA, UC, CD
Peficitinib	JAK3	RA
PF-04965842	JAK1	Atopic dermatitis, Psoriasis
Gandotinib	JAK2	Myeloproliferative neoplasms
Lestaurtinib	JAK2	AML
Momelotinib	JAK1/JAK2	Myeloproliferative disorders, metastatic pancreatic cancer
Pacricitinib	JAK2	Relapsed lymphoma, advanced myeloid malignancies, myelofibrosis, myeloproliferative neoplasms, MDS
Fedratinib	JAK2	Primary myelofibrosis, PCV, essential thrombocythemia

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JAK Inhibitors For RA

PHARMAKOKINETICS

	TOFACITINIB	BARICITINIB
Mode of action:	JAK1, JAK3, (JAK2)	JAK1, JAK2
Indication:	Mono therapy or in combination with MTX or other csDMARDs	Mono therapy or in combination with MTX
Dosing	5 mg BID	4 mg QD
Elimination:	Hepatic	Renal
Reduced dose:	Moderate liver impairment	Moderate kidney impairment Age >75 yrs
Drug interactions:	CYP3A4, CYP2C (Clarithromycin, Ketoconazole ...)	OAT3 (Probenecid)
Recommended lab tests:	Neutrophils, leukocytes, Hgb, transaminases, lipids	Neutrophils, leukocytes, Hgb, transaminases, lipids, creatinine

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JAK Inhibitors For RA

SAFETY

INFECTIONS IR (100 pt. years)	TOFACITINIB ¹	BARICITINIB ²
Serious infections	2.7	3.2
Herpes zoster	3.9	3.4
Herpes zoster serious	0.3	0.5 ³

1) Cohen et al. Ann Rheum Dis. 2017

2) Genovese et al. ACR 2017; poster 511

3) Eli Lilly data on file

MALIGNANCIES IR (100 pt. years)	TOFACITINIB ¹	BARICITINIB ²
Malignancies (excl. NMSC)	0.9	0.8

1) Cohen et al. Ann Rheum Dis. 2017

2) Genovese et al. ACR 2017; poster 511

Asthma

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Asthma Market Size

Global Market for Allergy Treatment Products, by Type, Through 2021
(\$ Millions)

Product Type	2015	2016	2021	CAGR% 2016–2021
Prescription	12,814	14,329	17,583	4.2
Generic	8,940	10,354	17,494	11.1
OTC	8,046	8,717	9,324	1.4
Total	29,800	33,400	44,401	5.9

OTC, over-the-counter.

Source: BCC Research; ALK-Abelló; Ranbaxy; Meda AB.

Table 5-9: Asthma mAb Market, 2017-2022 (\$ millions)

	2017 \$	2022 \$	GAGR 2017-2022
Asthma mAb Sales	\$ 3,204	\$ 5,170	10.0

Source: Kalorama Information

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Asthma Competitive Landscape

- **Competitive landscape**
 - **Fasenra (Benralizumab) IL 5 receptor**
 - **Nucala (Mepolizumab) IL 5**
- **IL 13 Inhibition for Asthma**
 - Dupilumab (IL 4/13 inhibition via IL4ra) is effective
 - Tralokinumab (IL-13 inhibition), while initially promising, has [MIXED results](#)

Competitor Landscape

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Products in the Atopic Dermatitis Market

Company	Drug Name	Mechanism of Action (Application)	Status	Sales
Regeneron and Sanofi	Dupilumab (Dupixent)	IL-4Ra inhibition, for IL-4 and IL-13 inhibition (injection)	Approved and Sold for Eczema, Nasal Polyps, and Asthma	1.871B in US, 2.3B Global, eventual sales of 10B projected (at margins approaching ~30%)
Lilly	Olumiant (Baricitinib)	JAK1/2 oral inhibitor	Phase III for AD, Sold for RA	
AbbVie	Rinvoq (upadacitinib)	JAK-1 oral inhibitor	Phase III for AD	
Pfizer	Xeljanz (tofacitinib)	JAK1/3 inhibitor that Inhibits IL-14 and other molecules (topical/oral)	Phase 3 trials almost done for AD. Sold for adults with moderately to severely RA, Psoriatic arthritis, and ulcerative colitis	n/a
Pfizer	Abrocitinib	JAK1 inhibitor	Phase 3 trials almost done	n/a
Dermira (Eli Lilly)	Lebrikizumab	IL-13 Inhibition (Injection)	Phase 3 trials underway	n/a
Leo Pharma	Tralokinumab	IL-13 Inhibition (Injection)	Phase 3 Trials Wrapping Up	n/a
Asana Biosciences	AsN002	JAK/SYK Inhibitor	Phase II	

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Products in the Asthma Market

Company	Drug Name	Mechanism of Action	Status	Sales
Regeneron and Sanofi	Dupixent (Dupilumab)	IL-4Ra inhibition, for IL-4 and IL-13 inhibition	Approved and Sold for Adult Eczema, Nasal Polyps, and Asthma On track for approval for eosinophilic esophagitis (EOE), Pediatric Asthma, Pediatric AD	1.871B in US, 2.3B Global, eventual sales of 10B projected 30% of these sales are from Asthma REGN - Stock Business Line Segments
Dermira (Eli Lilly)	Lebrikizumab	IL-13 Inhibition	Abandoned for lack of efficacy	n/a
Leo Pharma	Tralokinumab	IL-13 Inhibition	Lack of efficacy	n/a
MedImmune (Astra Zeneca)	Fasenra (Benralizumab)	IL-5R Inhibition	Approved in 2017 by FDA for severe eosinophilic asthma 2019 for eosinophilic oesophagitis	~\$297 Million in its first year of sales for Asthma
GSK	Nucala (Mepolizumab)	IL-5 Inhibition	Approved by FDA for Severe Asthma for patients 6 and older	£563 annual sales in 2018

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Products in the Rheumatoid Arthritis Market

Company	Drug Name	Mechanism of Action	Status	Sales
Pfizer	Xeljanz (tofacitinib)	JAK1/3 inhibitor that decreases IL-4 (Oral)	Sold for adults with moderately to severely RA, Psoriatic arthritis, and ulcerative colitis	2.24Bn global sales (Consider this sale number includes other indications other than RA) PFE Stock Business Revenue Segments
Eli Lilly	Olumiant (baricitinib)	JAK1/2 inhibitor (oral)	Approved for RA adult patients with moderately to severely active RA who have had an inadequate response to TNF antagonists. Being tested for AD	426.9Mn in 2019 Global sales
AbbVie	Rinvoq (upadacitinib)	(oral) JAK1 inhibitor	Approved for RA. Phase 3 trials for atopic dermatitis, psoriatic arthritis, Crohn's disease, and ulcerative colitis	Aug-Dec sales in 2019 = 47M (approved for sale in August)
Gilead Sciences, Inc.	Filgotinib	JAK1 inhibitor	Being investigated, clinical trials underway	n/a
Company	Drug Name	Mechanism of Action	Status	Sales

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Sample Drug for RA: Xeljanz (tofacitinib)

Approved:

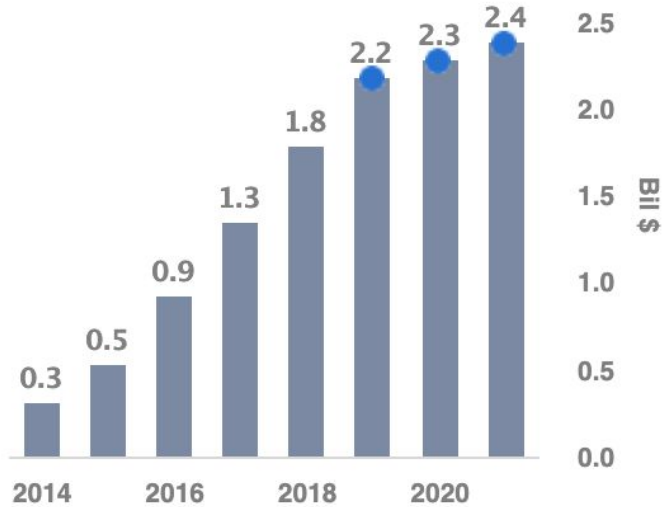
- Pfizer's **Xeljanz (tofacitinib)**, a pan-JAK inhibitor
 - Approved Nov 2012
 - **Oral intake**
 - **Accounts for 4% of the total RA market**
 - Protected against biosimilar competition until 2025
 - Sales of more than \$1.6bn/year
- Price of topical tofacitinib: 320\$/bottle, lasts 90 days.
 - \$2,326.53, 28% off the average retail price of \$3,270.55 for 30 tablets



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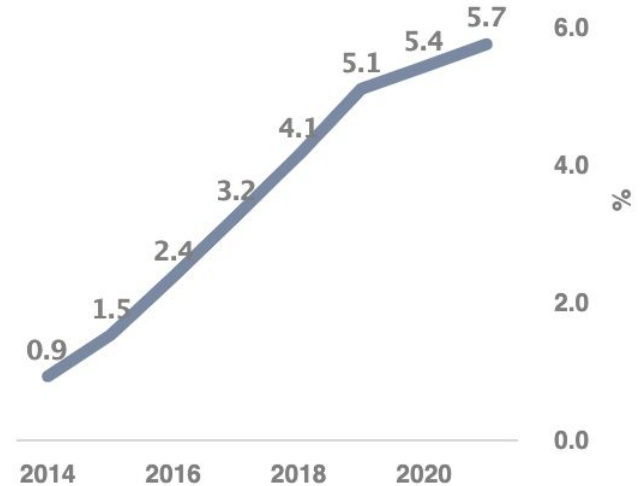
Sample Drug for RA: Xeljanz (tofacitinib)

Xeljanz (Pfizer)



Revenue Growth

Xeljanz's Share In Global Rheumatoid Arthritis



Market Share Growth

IL-13 Inhibition Is Ineffective for Asthma

AstraZeneca's asthma drug tralokinumab goes 0 for 3 in PhIII as 2 more trials flop

You can write off just about all of the remaining value assigned to AstraZeneca's asthma drug tralokinumab — if you hadn't already done so. Outside of the cancer arena, AstraZeneca's string of setbacks is continuing.

The pharma giant followed up yesterday's news that its BTK drug Calquence (acalabrutinib) had scored an early approval at the FDA with a note writing off the last two Phase III studies of their IL-13 drug tralokinumab as failures.

Roche sells off its struggling IL-13 drug lebrikizumab in \$1.4B Dermira deal

After watching its late-stage asthma program for its IL-13 drug lebrikizumab flounder with mixed and markedly unimpressive results, Roche is outlicensing the bulk of the development rights to Dermira [\\$DERM](#) in a \$1.4 billion deal — which starts off with \$135 million in near-term cash.

Dermira is planning to hustle its new drug directly into a Phase IIb study for atopic dermatitis so it can line up a dose as quickly as possible that researchers can take into Phase III.