Novartis R&D Day

December 2, 2021
## R&D Day 2021
December 2, 2021 (CET times)

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
</tr>
</thead>
<tbody>
<tr>
<td>14.00 – 14.50</td>
<td><strong>Novartis Strategy and Growth Story</strong></td>
</tr>
<tr>
<td>14.50 – 15.30</td>
<td><strong>Cardiovascular and Renal</strong></td>
</tr>
<tr>
<td>15.30 – 15.50</td>
<td>Break</td>
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<tr>
<td>15.50 – 16.45</td>
<td><strong>Immunology, Hepatology and Dermatology</strong></td>
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<tr>
<td>16.45 – 17.10</td>
<td><strong>Neuroscience</strong></td>
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<tr>
<td>17.10 – 17.30</td>
<td>Break</td>
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<tr>
<td>17.30 – 18.20</td>
<td><strong>Oncology</strong></td>
</tr>
<tr>
<td>18.20 – 18.50</td>
<td><strong>NIBR and Technology Platforms</strong></td>
</tr>
<tr>
<td>18.50 – 19.00</td>
<td><strong>Closing</strong></td>
</tr>
</tbody>
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**References**

**Submission schedules**

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**Appendix**

**Respiratory & Allergy**

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**NIBR and Technology Platforms**

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**Neuroscience**

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**Oncology**

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**Cardiovascular and Renal**

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**Immunology, Hepatology & Dermatology**

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**Novartis Strategy and Growth Story**

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Speakers

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CFO, Novartis

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President, Novartis Pharmaceuticals

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Global Head, Neuroscience Development Unit

Jeff Legos
Global Head, Oncology Development Unit

Alice Shaw
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Jay Bradner
President, Novartis Institutes for BioMedical Research (NIBR)
Novartis Strategy and Growth Story
Our strategy
Focused medicines company powered by technology leadership in R&D, world-class commercialization, global access and data science

Where to play | our focus

- Strengthen our core therapeutic areas
- Accelerate our 4 priority geographies

How to win | our five priorities

- Embrace operational excellence every day
- Deliver transformative innovation
- Go big on data and digital
- Unleash the power of our people
- Build trust with society

Our aspiration

- Innovation power
  - Top 3 innovator
- Growth
  - Consistent above peer median average growth
- ESG
  - Global leader in material ESG factors
- Returns
  - High 30s IM margin, attractive ROIC

1. Return on invested capital.
Today, we are a fully focused medicines company delivering consistent top-line growth with margin expansion

### Diversified Healthcare Group

**1996 - 2014**

### Focused Medicines Company

**2015 - 2021**

#### Actions 2015 – 2020

- Exit of Animal Health, Vaccines, Consumer Health
- Alcon spin | value creating, tax neutral, largest in EU market history
- Opportunistic bolt-on acquisitions

#### Actions 2021

- Strategic Review of Sandoz to maximize shareholder value
- Sale of Roche stake | single bilateral transaction, ~USD 21bn, no tax leakage, IRR of 10.2% in USD

#### Consistent strong operating performance (Innovative Medicines)

**Sales**

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>25.9</td>
<td>27.8</td>
<td>28.8</td>
<td>31.3</td>
</tr>
</tbody>
</table>

**Core OpInc**

<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>8.4</td>
<td>9.5</td>
<td>10.4</td>
<td>11.6</td>
</tr>
</tbody>
</table>

**Innovative Medicines**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>32.4</td>
<td>34.3</td>
<td>36.3</td>
<td>37.1</td>
</tr>
</tbody>
</table>
We remain disciplined and shareholder-focused in our capital allocation priorities

Capital allocation priorities

1. Investments in organic business
   - Continued focus on core medicines business

2. Growing annual dividend in CHF
   - Committed to maintain strong and growing dividend (in CHF), increased by CAGR 7.8% in CHF and 9.8% in USD between 1996-2020

3. Value-creating bolt-ons
   - ~USD 29bn M&A bolt-ons since 2018 (10+ deals, mean of ~USD 2bn)

4. Share buybacks
   - ~USD 12bn of share buybacks over past 5 years

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1. Reflecting dividend payments up to and including the business year 2020 (paid out in March 2021), converted at historic exchange rates at the respective dividend payment dates as per Bloomberg.  
2. Until Q3 2021.  
We have therapeutic area depth, strength in technology platforms, and a balanced geographic presence

In-market and pipeline depth in 5 therapeutic areas

<table>
<thead>
<tr>
<th>Therapeutic Area</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRM, IHD, NS, ONC, HEM</td>
<td>Opportunistic in others: Ophthalmology &amp; Respiratory</td>
</tr>
<tr>
<td>In-market blockbuster assets</td>
<td>14</td>
</tr>
<tr>
<td>Potential bn-USD+ pipeline assets with approval by 2026</td>
<td>20</td>
</tr>
<tr>
<td>Limited binary risk on a single product</td>
<td>8%</td>
</tr>
</tbody>
</table>

Strong positions in technology platforms

<table>
<thead>
<tr>
<th>Technology Platform</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPD</td>
<td>Advance our broad portfolio of NMEs</td>
</tr>
<tr>
<td>CELL THERAPY</td>
<td>Lead in next generation of CAR-Ts</td>
</tr>
<tr>
<td>GENE THERAPY</td>
<td>Advance next wave of assets</td>
</tr>
<tr>
<td>RLT</td>
<td>Expand across additional solid tumors</td>
</tr>
<tr>
<td>xRNA</td>
<td>Fully build up siRNA capabilities</td>
</tr>
</tbody>
</table>

Geographically diversified

1. Cardio-Renal, Immunology, Neuroscience, Oncology, Hematology 2. Based on 2020 Group sales actuals 3. Source IQVIA Analytics Link (MIDAS database), sales numbers are estimated bottom up based on average wholesaler price and volume, and therefore deviates from net sales reported by companies in their annual reports. Includes branded and generics drugs as well as vaccines but no OTC. 4. Relative to peers. TPD: Targeted Protein Degradation, RLT: Radioligand Therapy.
Our innovative pipeline addresses unmet medical needs with a renewed focus to deliver high value assets

<table>
<thead>
<tr>
<th>Scale</th>
<th>Innovation</th>
<th>Value</th>
<th>Priorities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Projects¹</td>
<td>~85% Pipeline² potentially first-in-class / first-in indication</td>
<td>~1.5x eNPV growth per asset since 2017⁴</td>
<td>Early expansion into multiple indications (e.g. Iptacopan, Remibrutinib, Ligelizumab)</td>
</tr>
<tr>
<td>70 NMEs</td>
<td>&gt;80% Target areas of high unmet need²</td>
<td>#1 NME US FDA approvals³</td>
<td>Rapid transitions to pivotal studies especially for high value assets (e.g. JDQ/TNO, NIS, YTB)</td>
</tr>
<tr>
<td>65 Phase 3 / Registration</td>
<td></td>
<td>² Confirmatory Development Pipeline eNPV</td>
<td>Early out licensure of non-strategic internal assets</td>
</tr>
<tr>
<td>100 Phase 1/2</td>
<td>⁴ Confirmatory development pipeline.</td>
<td></td>
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</tr>
</tbody>
</table>

Novartis is committed to driving consistent growth through 2030 and beyond

**IM sales evolution**
Illustrative, USD billion, % CAGR cc

1. **2020-2026 | ≥4%**
   - Focused resources on key growth brands and launches, upscaling next generation engagement models

2. **2026-2030 | >peer median**
   - Double-down on internal pipeline assets to unlock their full potential and add complementary BD&L

3. **>2030 | >peer median**
   - Focused investments in technology platforms while staying at the forefront of innovation in small and large molecules

1. 6% in USD
Novartis Growth Story

2020 - 2026
Six assets with multi-billion USD sales potential to drive growth

<table>
<thead>
<tr>
<th>Q3 sales annualized¹</th>
<th>Peak sales CAGR 2020-2026</th>
</tr>
</thead>
<tbody>
<tr>
<td>USD bn</td>
<td>USD bn</td>
</tr>
<tr>
<td>5.0</td>
<td>7.0</td>
</tr>
<tr>
<td>+22%</td>
<td>Low double-digit</td>
</tr>
<tr>
<td>Q3 Growth</td>
<td>USD bn</td>
</tr>
<tr>
<td>USD bn</td>
<td>USD bn</td>
</tr>
<tr>
<td>&gt;7.0</td>
<td>Multi-billion³</td>
</tr>
<tr>
<td>Low double-digit</td>
<td>Low to mid teens</td>
</tr>
<tr>
<td>US LoE²</td>
<td>2029+</td>
</tr>
</tbody>
</table>

USD, all growth rates in constant currencies (cc). Excludes potential impact from US HC reform. 1. Reported Q3 net sales annualized. 2. Estimated based on relevant patents; further extensions possible. 3. Including Zolgensma IT. 4. Including Kisqali adjuvant.
Leqvio® on track for US launch with FDA action date January 1

US launch preparation on track
Enable ~200 prioritized health systems readiness
Drive awareness among HCPs leveraging strong CV footprint
Facilitate product acquisition through >1000 AICs

Generating additional evidence
V-INITIATE Explore “Leqvio® first” directly after statins
V-INCEPTION Investigate Leqvio® initiation after ACS events

Ex-US launches continue
RoW | Approved in 50 countries, reimbursement reviews in >10 markets
UK | NHS population health agreement to treat ~300k ASCVD patients

1. Alternative Injection Centers. 2. In patients with elevated LDL-C despite treatment with maximally tolerated statin therapy. V-INITIATE NCT04929249; V-INCEPTION NCT04873934.
Additional key 2022 launches include Scemblix® and ¹⁷⁷Lu-PSMA-617

First STAMP inhibitor in 3L CML
FDA approval received in 3L CML and CML patients with T315I mutation
~25% of all CML patients addressable with current label

Potential to provide best benefit-risk profile in 1L CML
>50% of patients treated front line with imatinib develop resistance or intolerance
30-40% treated with 2nd generation TKIs

Initiated 1L pivotal study of asciminib vs. investigator-selected TKI (FPFV¹ achieved in Q4 2021)

¹⁷⁷Lu-PSMA-617

Prognosis remains poor for patients with mCRPC³
2nd most diagnosed cancer in men
>80% of patients metastatic at the time of CRPC diagnosis
~10 months median OS on available treatment options

With FDA Priority Review, PDUFA⁴ expected H1 2022
Submitted ⁶⁸Ga-PSMA-11 kit for PET imaging to FDA
Scaling community centers on RLT
EMA submission completed and approval expected in H1 2022

1. First patient first visit. 2. Product and brand name are currently under FDA review. 3. Metastatic castration-resistant prostate cancer. 4. Prescription Drug User Fee Act.
Growth drivers and pipeline expected to exceed estimated USD 9bn gap from new generic entries through 2026

**Sales from products with future Gx competition**

Illustrative, USD billion @cc
Assumptions including Entresto US LoE (2025)¹

<table>
<thead>
<tr>
<th>2020</th>
<th>2026</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>7</td>
</tr>
</tbody>
</table>

Gap to fill: ~9bn

**USD 9bn**

**Generic gap**

≥USD 2.5bn  
Potential upside to 2026 sales  
If Entresto US LoE is beyond 2026¹

Given our global footprint, LoE and erosion curves vary between geographies

**Significant potential sales** for major brands remain for some time post genericization, e.g., Diovan family, Glivec

Products with future Gx impact up to 2026: Entresto, Lucentis, Gilenya, Tasigna, Promacta, Sandostatin, Xolair, Afinitor, Q-Family and Votrient

Excludes potential impact from US healthcare reforms and decline of established medicines & existing generics

¹ For internal forecasting purposes we do not expect Gx in US at least until 2025
Confident in delivering 4%+ sales CAGR 2020 - 2026

Illustrative Group sales
USD billion, cc

Excludes potential impact from US healthcare reform

\[ \text{IM Core Margin} \times \text{Future Gx impact up to 2026} \]

\[ \text{In-market growth drivers / base business} \]

\[ \text{IM Division pipeline probabilized} \]

\[ \text{2020} \]

\[ -9 \]

Tasigna
Lucentis
Xolair
Sandostatin
Gilengya
Afinitor
Entresto

\[ \text{Without any pipeline contribution} \]

\[ \text{IM Core Margin} 35\% \]

\[ \text{2026} \]

\[ ~+4\% \text{ CAGR cc} \]

Leqvio
Lu-PSMA-617
Scemblix
Ligelizumab
Other pipeline

\[ \text{IM Core Margin} \]

High 30s

1. Estimated based on relevant patents; further extensions possible. Additional products include Promacta, Q-Family and Votrient.
2. For internal forecasting purposes we do not expect Gx in US at least until 2025.
In summary – our growth story to 2026

2020-2026 Sales Group CAGR (cc)

+1.5%  Overcoming USD 9bn Gx erosion gap and assuming zero contribution from pipeline

~+3%¹  Current consensus

+4%  Our expectations with probabilized pipeline sales and Entresto LoE forecast assumption of 2025²

+5%  Our expectations with probabilized pipeline sales and potential Entresto LoE beyond 2026²

1. 2.7%-3.1% based on In-house, FactSet, Bloomberg consensus  
2. For internal forecasting purposes we do not expect Gx in US at least until 2025
Novartis Growth Story

2026 - 2030
## Up to 20 potential billion-USD+ pipeline assets with approval by 2026

Most are supported by high strength of evidence

### Selected assets

<table>
<thead>
<tr>
<th>Strength of evidence</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unprobabilized peak sales USD bn / multi-bn</strong></td>
<td>Sabatolimab MDS, AML</td>
<td>Iptacopan PNH, C3G, IgA, aHUS</td>
</tr>
<tr>
<td></td>
<td>NIS973 PDAC, Colorectal Cancer</td>
<td>Remibrutinib CSU, NS</td>
</tr>
<tr>
<td></td>
<td>Pelacarsen CVRR</td>
<td>Rollepsin MAH, ScL, RA</td>
</tr>
<tr>
<td></td>
<td>Canakinumab Adj, NSCLC</td>
<td>Leqvio Hypercholesterolemia</td>
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<tr>
<td></td>
<td>UNR844 Presbyopia</td>
<td>Kysqali Adj, SC (+endocrine th.)</td>
</tr>
<tr>
<td></td>
<td>Libvatre (SAF312) Chronic Ocular Surface Pain</td>
<td>YTB323, 2L DLBCL</td>
</tr>
<tr>
<td></td>
<td>TNO155, JDQ443* NSCLC; Colorectal Cancer; Combos</td>
<td>Ilabelumab Sjogren's, SLE, AIH; Lupus Nephritis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Strength of evidence</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unprobabilized peak sales up to USD 1bn</strong></td>
<td>Lutathera 1L G2/G3 NET</td>
<td>Kymriah r/r Follicular Lymphoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Beovu DME</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tafinlar/Mekinist Solid tumor Agnostic</td>
</tr>
</tbody>
</table>

1. Ph3 to start in 2022. Assets are shown in the phase of the most advanced indication (listed first). Value based on the total of the listed indication(s). Strength of evidence based on the most advanced indication: High if in Ph3 or when Ph2 results available for the same MoA in the lead indication.

Most advanced and key indication(s) approved by 2026

- Submission
- Phase III
- Phase II
- LCM

### Respiratory & Allergy

- Iptacopan PNH; C3G; IgA; aHUS
- Kisqali Adj, BC (+endocrine th.)

### Cardiovascular and Renal

- Leqvio Hypercholesterolemia
- Cosentyx Multiple indications
- Ilabelumab Sjogren's, SLE, AIH; Lupus Nephritis

### Immunology, Hepatology & Dermatology

- Tafinlar/Mekinist Solid tumor Agnostic
- Beovu DME
- Tafinlar/Mekinist Solid tumor Agnostic
- Jakavi SR GvHD

### Neuroscience

- Lutathera 1L G2/G3 NET
- Kymriah r/r Follicular Lymphoma
- Tafinlar/Mekinist Solid tumor Agnostic
- Jakavi SR GvHD

### Oncology

- Lutathera 1L G2/G3 NET
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- Beovu DME
- Tafinlar/Mekinist Solid tumor Agnostic
- Jakavi SR GvHD

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- Beovu DME
- Tafinlar/Mekinist Solid tumor Agnostic
- Jakavi SR GvHD

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- Iptacopan PNH; C3G; IgA; aHUS
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- Cosentyx Multiple indications
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### Oncology

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- Tafinlar/Mekinist Solid tumor Agnostic
- Jakavi SR GvHD

### NIBR and Technology Platforms

- Lutathera 1L G2/G3 NET
- Kymriah r/r Follicular Lymphoma
- Beovu DME
- Tafinlar/Mekinist Solid tumor Agnostic
- Jakavi SR GvHD
Promising pipeline assets to drive mid-term growth (1/2)
Pharmaceuticals

Selected assets, nearly all with exclusivity into 2030+

### Cardio-Renal

<table>
<thead>
<tr>
<th>Asset</th>
<th>Indication</th>
<th>Peak Sales</th>
<th>Next Milestone/ Status</th>
<th>Submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leqivo</td>
<td>Hyperlipidemia</td>
<td>● ● ● ● ●</td>
<td>FDA action date Jan 1st 2022</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CVRR-LDLC</td>
<td>● ● ● ● ●</td>
<td>Ph3 ORION-4 and VICTORIAN-2-PREVENT ongoing</td>
<td>2026+</td>
</tr>
<tr>
<td>Iptacoplan1</td>
<td>IgAN</td>
<td>● ● ● ● ●</td>
<td>Ph3 APPLAUSE-IgAN ongoing</td>
<td>2023+</td>
</tr>
<tr>
<td></td>
<td>C3G</td>
<td>● ● ● ● ●</td>
<td>Ph3 APPEAR-C3G ongoing</td>
<td>2023</td>
</tr>
<tr>
<td></td>
<td>IMN</td>
<td></td>
<td>Ph2b ongoing</td>
<td>2026+</td>
</tr>
<tr>
<td>Pelacarsen</td>
<td>CVRR-Lp(a)</td>
<td>● ● ● ● ●</td>
<td>Ph3 ongoing</td>
<td>2025</td>
</tr>
</tbody>
</table>

### Immunology

<table>
<thead>
<tr>
<th>Asset</th>
<th>Indication</th>
<th>Peak Sales</th>
<th>Next Milestone/ Status</th>
<th>Submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cosentyx</td>
<td>HS</td>
<td></td>
<td>Ph3 SUNRISE, SUNSHINE positive readout H2 2021</td>
<td>2022</td>
</tr>
<tr>
<td>GCA</td>
<td></td>
<td></td>
<td>Ph3 ongoing</td>
<td>2024</td>
</tr>
<tr>
<td>jPsA/ERA</td>
<td></td>
<td></td>
<td>In registration</td>
<td></td>
</tr>
<tr>
<td>Lupus Nephritis</td>
<td></td>
<td></td>
<td>Ph3 SELUNE ongoing</td>
<td>2026+</td>
</tr>
<tr>
<td>Lichen Planus</td>
<td></td>
<td></td>
<td>Ph2b PRELUDE readout in 2022</td>
<td>2025</td>
</tr>
<tr>
<td>Ligilizumab</td>
<td>CSU</td>
<td></td>
<td>Ph3 PEARL 1, 2 readout 2021</td>
<td>2022</td>
</tr>
<tr>
<td></td>
<td>Food allergy4</td>
<td>● ● ● ● ●</td>
<td>Ph3 PEANUT start H2 2021</td>
<td>2025</td>
</tr>
<tr>
<td></td>
<td>CINDU</td>
<td></td>
<td>Ph3 PEARL-PROVOKE ongoing</td>
<td></td>
</tr>
<tr>
<td>Remibrutinib2</td>
<td>CSU</td>
<td>● ● ● ● ●</td>
<td>Ph3 REMIX-1 ongoing</td>
<td>2024</td>
</tr>
<tr>
<td></td>
<td>Other indications being explored</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

### Neuroscience

<table>
<thead>
<tr>
<th>Asset</th>
<th>Indication</th>
<th>Peak Sales</th>
<th>Next Milestone/ Status</th>
<th>Submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zolgensma</td>
<td>SMA IT</td>
<td>● ● ● ● ●</td>
<td>Ph3 STEER initiating</td>
<td>2025</td>
</tr>
<tr>
<td>Branaplan</td>
<td>Huntington’s disease</td>
<td>● ● ● ● ●</td>
<td>Ph2b start H2 2021</td>
<td>2026+</td>
</tr>
<tr>
<td>Remibrutinib1</td>
<td>Multiple sclerosis</td>
<td>● ● ● ● ●</td>
<td>Ph3 REMODEL-1 and 2 start H2 2021</td>
<td>2025</td>
</tr>
</tbody>
</table>

Unprobaiblized peak sales (USD): ● <1bn ● 1-2bn ●● >2bn

1. Peak sales potential based on all studied indications. 2. Based on 9 months UPCR readout (US accelerated approval). 3. Q4/2021-Q1/2022 potential COVID-19 impact. 4. Food Allergy indication falls within the Respiratory & Allergy therapeutic area.
### Promising pipeline assets to drive mid-term growth (2/2)

**Oncology**

Selected assets, nearly all with exclusivity into 2030+

#### Solid Tumors

<table>
<thead>
<tr>
<th>Asset</th>
<th>Indication</th>
<th>Peak Sales</th>
<th>Next Milestone/ Status</th>
<th>Submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kisqali</td>
<td>HR+/HER2- BC (adj)</td>
<td>● ● ●</td>
<td>Ph3 NATALEE readout event-driven, expected end 2022!</td>
<td>2023</td>
</tr>
<tr>
<td>Canakinumab</td>
<td>NSCLC adjuvant</td>
<td>● ● ●</td>
<td>Ph3 CANOPY-A readout in 2022</td>
<td>2023</td>
</tr>
<tr>
<td>Lu-PSMA-617</td>
<td>mCRPC post-taxane</td>
<td>● ● ●</td>
<td>In registration</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>mCRPC pre-taxane</td>
<td>● ● ●</td>
<td>Ph3 PSMAfore ongoing</td>
<td>2023</td>
</tr>
<tr>
<td></td>
<td>mHSPC</td>
<td>● ● ●</td>
<td>Ph3 PSMAAddition ongoing</td>
<td>2024</td>
</tr>
<tr>
<td>JDQ443</td>
<td>2/3L NSCLC (mono)</td>
<td>● ● ●</td>
<td>Ph3 start in H1 2022</td>
<td>2024</td>
</tr>
<tr>
<td></td>
<td>NSCLC (combo)</td>
<td>● ● ●</td>
<td>In Ph2</td>
<td>2026+</td>
</tr>
<tr>
<td>TNO155</td>
<td>SHP2 inhibitor</td>
<td>Solid tumors: multiple combinations being explored in ongoing trials</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tislelizumab</td>
<td>2L esophageal cancer</td>
<td>● ● ●</td>
<td>In registration</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>NSCLC</td>
<td>Multiple other indications</td>
<td>Ongoing trials</td>
<td></td>
</tr>
</tbody>
</table>

#### Hematology

<table>
<thead>
<tr>
<th>Asset</th>
<th>Indication</th>
<th>Peak Sales</th>
<th>Next Milestone/ Status</th>
<th>Submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scemblix</td>
<td>CML 3L</td>
<td>● ● ●</td>
<td>US approved</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>CML 1L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ph3 ongoing</td>
</tr>
<tr>
<td>Iptacopan²</td>
<td>PNH</td>
<td>● ● ●</td>
<td>Ph3 ongoing</td>
<td>2023</td>
</tr>
<tr>
<td></td>
<td>aHUS</td>
<td></td>
<td></td>
<td>Ph3 ongoing</td>
</tr>
<tr>
<td>Sabatolimab</td>
<td>HR-MDS</td>
<td>● ● ●</td>
<td>Ph2 STIMULUS-MDS-1 continues to PFS readout³</td>
<td>2022/2023</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ph3 STIMULUS-MDS-2 ongoing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AML</td>
<td></td>
<td>Ph2 STIMULUS-AML-1 ongoing</td>
<td>2024</td>
</tr>
<tr>
<td>YTB323</td>
<td>Non-Hodgkin's Lymphoma</td>
<td>● ● ●</td>
<td>Ph3 start 2022</td>
<td>2024</td>
</tr>
<tr>
<td></td>
<td>CD19 CAR-T</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHE885</td>
<td>BCMA CART-T</td>
<td>Multiple myeloma</td>
<td>Ph2 start 2022</td>
<td>2024</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Unprobabilized peak sales (USD): ● <1bn ● 1-2bn ● ● ● >2bn

2. Peak sales potential based on all studied indications.
3. Planned DMC readout for CR completed, study continues blinded to PFS readout, with submission in 2022/2023 using PFS and/or OS outcomes of Ph2 and/or Ph3 trial.
Recent data releases support progression of our mid-stage pipeline

**Cosentyx HS**
Primary efficacy endpoint was met in both Ph3 studies SUNSHINE and SUNRISE

**Iptacopan**
- C3G: 45% proteinuria reduction; EMA PRIME
- PNH: Ph2 substantial reduction in intra- & extravascular hemolysis; FDA BTD

**JDQ443**
Entering Ph3 2L KRAS G12C mutant NSCLC in H1 2022, based on ongoing Ph1 study

**Ianalumab**
Sjögren’s Ph2b primary endpoint met, confirming efficacy and good tolerability

**Remibrutinib**
Rapid and effective CSU disease activity control, with favorable safety in Ph2b

**YTB323 / PHE885**
T-Charge™ assets to be presented at ASH
  - Anti-CD19 YTB to Ph3
  - Anti-BCMA PHE to Ph2

**Branaplam**
Potential FIC† for Huntington’s Ph2b initiated based on demonstrated PoC in pre-clinical, Ph1 (healthy volunteers) and SMA studies

---

1. First-in-class.
Novartis Growth Story

2030 and beyond
The Biopharmaceutical industry is shifting towards new platforms to find the next wave of medicines and we are investing to lead

Global pipeline composition, directional technology outlook

Novartis portfolio shift towards biologics & advanced platforms

1. Microbiome, Nanotechnologies, Bioelectronics, Bioengineered vaccines, Protein extracts. 2. Currently ~60% of global clinical pipeline. 3. Targeted Protein Degradation. Source: McKinsey analysis, EvaluatePharma

Expand platforms:
- Cell therapy
- Gene therapy
- Radioligand therapy
- xRNA therapy

Scale biologics

Focus on new approaches to address previously intractable targets with small molecules, (e.g., TPD³)
We take a principled approach to selecting platforms and deploying them in our core therapeutic areas

### Principles for platform investments

- Broad applicability
- Clear differentiation
- Advances disease area strategy
- Scalability
- Integration of diverse expertise
- Sustained competitive advantage

### Major Novartis platforms

- Chemistry & Chemical Biology | TPD
- Biotherapeutics | xRNA
- Stem-Progenitor Cell Therapy
- Viral Gene Therapy
- Radioligand Therapy

### Applying our technology across other TAs

<table>
<thead>
<tr>
<th>Biotherapeutics</th>
<th>Cell</th>
<th>Gene</th>
<th>RLT</th>
<th>xRNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncology</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Cardio-Renal</td>
<td></td>
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<tr>
<td>Immunology</td>
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<tr>
<td>Neuroscience</td>
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<tr>
<td>Ophthalmology</td>
<td></td>
<td></td>
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<tr>
<td>Respiratory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Targeted Protein Degradation
2. xRNA includes RNA targeting LMWs, ASOs, siRNA, mRNA cancer vaccines.

Currently marketed products
Potential to expand
Advancing our biologics / xRNA capabilities to realize new therapeutic opportunities

Selected technologies, not a comprehensive list

**Marketed portfolio**
Capturing value from validated technology

**Marketed monoclonal antibodies**
Established and proven approach, binds single target

Potential additional indications

- **Cosentyx**
- **ILARIS**

15 products on the market

**Clinical portfolio**
Scaling new therapeutic approaches to the clinic

**Peptide therapeutic**
(\text{LNA043})

**Antisense therapy**
(Pelacarsen)

**ANGPTL3 agonist for osteoarthritis**

- Anti-sense oligo
- Bind mRNA blocking translation
- Reduced protein levels

~70 projects

**Discovery pipeline**
Innovating emerging technology

**Antibody drug conjugates**

Localize payload (small molecule, RNA, radiolabel, etc.) to the Ab’s target

**Multi-specific and multi-chain**
Chimeric biomolecules with high specificity to modulate complex biology (e.g. tolerance, anergy)

~50 projects

---

1. Based on 2020 Actuals. 2. Clinical development Ph1 to submission.
### Continue innovating on small molecules while building strong position in new technology platforms

<table>
<thead>
<tr>
<th>TPD</th>
<th>Cell</th>
<th>Gene</th>
<th>RLT</th>
<th>xRNA&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Existing commercial assets</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>KYMRIAH</td>
<td>zolgensma&lt;sup&gt;®&lt;/sup&gt;</td>
<td>LUTATHERA&lt;sup&gt;®&lt;/sup&gt;</td>
<td>LEQVIO&lt;sup&gt;®&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Key focus</strong></td>
<td>Unlock previously undruggable targets</td>
<td>Enhance potency, durability and manufacturing efficiency</td>
<td>Explore novel cargos, targeting, and switchable expression</td>
<td>Expand the indication landscape</td>
</tr>
<tr>
<td># of projects&lt;sup&gt;2&lt;/sup&gt;</td>
<td>12</td>
<td>15</td>
<td>22</td>
<td>12</td>
</tr>
<tr>
<td>Expected next filing</td>
<td>2026+</td>
<td>2024</td>
<td>2025</td>
<td>2023</td>
</tr>
</tbody>
</table>

1. xRNA includes RNA targeting LMWs, ASOs, siRNA, mRNA cancer vaccines.
2. Exploratory to Ph1/2
We are a global leader in technical and production capabilities in advanced therapy platforms

Advanced therapies manufacturing footprint

North Americas

- Biologics (9)
  - Austria
  - Belgium
  - France
  - Slovenia
  - Singapore
  - Switzerland

- Cell therapy (3)
  - France
  - Switzerland
  - USA

- Gene therapy (2)
  - USA

Europe

- RNA (3)
  - Austria
  - Ireland
  - Switzerland

- RLT (5)
  - Italy
  - Netherlands
  - Spain

Asia

Scaled operations in biologics and advanced therapies

- Building leading supply network across Biologics, Cell therapy, Gene therapy, RNA and RLT
- Deep technical expertise enables support of internal pipeline and to be a partner of choice
- Growing CMO operations with multiple partnership agreements in place

Note: Number in parenthesis indicate count of Novartis’ own sites.
Novartis path to leadership in technology platforms
Building on the integrated technology platform strengths across our organization

Depth and breadth across platforms
~70 projects¹

Development and regulatory experience

Technology platforms

Manufacturing scale and expertise

Experience in commercialization

Global footprint

¹ Exploratory to Ph1/2
Harnessing the power of data science and AI, alongside external partners, to fuel longer-term growth

Launched Data42 as a data science platform to reimagine medicine, one of the most advanced platforms in the industry

Other examples include:
- Anchor data and AI partnership with enterprise-wide activities
- Digital healthcare solution across chronic heart disease and dermatology
- Develop next-generation patient services platform

- Data at our fingertips
  - 60% active users
  - Faster time to insights
- Clinical trials
  - ~2,700 harmonized
  - ~220 investigations conducted
  - ~700 users onboarded
- Days vs. years to find data
- Weeks vs. months to insights

~2,700 clinical trials
~220 investigations
~700 users
Key takeaways

1. Clear strategy
   Delivering on strategy as a focused medicines company

2. Attractive growth profile
   Confident in 4%+ sales CAGR (2020 to 2026) and above peer median beyond 2026

3. Strong mid-stage portfolio
   Breadth and depth, up to 20 assets with USD ≥1bn potential, fuel further growth to 2030 and beyond

4. Platform leadership
   Continue to develop leadership across technology platforms
Cardiovascular and Renal

Agenda
Speakers
Novartis Strategy and Growth Story
- Cardiovascular and Renal
  - Strategy
  - Leqvio®
  - Palicasen
  - Iptacopan
- Immunology, Hepatology & Dermatology
- Neuroscience
- Oncology
- NIBR and Technology Platforms
- Appendix
  - Respiratory & Allergy
  - Submission schedules
- References
Our CRM strategy is focused on areas of high unmet need, with a strong mid and late-stage pipeline

CRM strategy

- Novel approaches that fundamentally improve HF outcomes at scale
- Dyslipidemia treatments that improve CV morbidity/mortality in identifiable high-risk groups with high unmet need and leverage innovative commercial models
- New solutions for chronic and acute renal specialty indications with high unmet need and limited/no targeted therapies
- Disease modification therapies for metabolic disorders

Assets highlighted today:
Leqvio®, pelacarsen, iptacopan

<table>
<thead>
<tr>
<th>Compound (indication)</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Registration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leqvio® (Hyperlipidemia)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leqvio® (CVRR-LDLC)</td>
<td></td>
<td></td>
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<tr>
<td>Leqvio® (Primary Prevention)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Leqvio® (Ped hyperlipidemia)</td>
<td></td>
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<tr>
<td>Entresto® (Ped CHF)</td>
<td></td>
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</tr>
<tr>
<td>Pelacarsen (Lp(a))</td>
<td></td>
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<tr>
<td>HSY244 (AF)</td>
<td></td>
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</tr>
<tr>
<td>iptacopan (IgAN)</td>
<td></td>
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<tr>
<td>iptacopan (C3G)</td>
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<tr>
<td>iptacopan (aHUS)</td>
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<tr>
<td>iptacopan (MN)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>iptacopan (others)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>iscalimab (T1D)</td>
<td></td>
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<tr>
<td>MBL949 (Obesity)</td>
<td></td>
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</tr>
</tbody>
</table>

Disease area
- Cardio
- Renal
- Metabolic

Note: bars in Gantt chart indicate current phase of development. *Not yet started.
Key highlights

- More than 135m ASCVD patients worldwide and only ~20% reach LDL-C goal in real-world practice despite existing therapies\(^3,4,5\)
- Leqvio\(^1\) demonstrated effective and sustained LDL-C reduction up to 52% with only two doses a year\(^2,5\) and safety comparable to placebo
- Inclisiran is approved in 50 countries worldwide incl. EU and UK. US FDA review ongoing, launch preparation aligned with expected FDA action date January 1, 2022
- Poised to overcome access, affordability and adherence challenges based on unique product features (twice yearly dosing, HCP administration) and commercial model
- Comprehensive study program including expansion into primary prevention
- US/EU: Patents on composition of matter and use 2035-2036 / Patent on composition of matter 2035\(^6\)

Leqvio\(^1\)
(inclisiran)

First and only siRNA LDL cholesterol lowering treatment

Marketed (EU)
RNA interference: harnessing a natural process to target LDL-C and Lp(a)

Only ~2% of the human genome encodes proteins while a significant portion codes for **non-coding RNAs** (ncRNAs)

**ncRNAs are involved in gene regulation**, RNA maturation and protein synthesis

**Inclisiran** is a **small interfering RNA**
- Double strand (sense and antisense)
- RNA degradation through RISC
- GalNAc conjugated for targeted delivery to liver

**Pelacarsen** is an **antisense oligonucleotide**
- Single strand (antisense only)
- RNA degradation by RNase H1
- GalNAc conjugated for targeted delivery to liver
Despite availability of effective treatments, the burden of cardiovascular disease on health systems continues to rise

CVD accounts for more deaths than any other disease\(^1\)

<table>
<thead>
<tr>
<th>% of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular diseases 30%</td>
</tr>
<tr>
<td>Chronic respiratory diseases 7%</td>
</tr>
<tr>
<td>Other conditions 30%</td>
</tr>
<tr>
<td>Injuries 9%</td>
</tr>
<tr>
<td>Other chronic diseases 9%</td>
</tr>
<tr>
<td>Cancer 13%</td>
</tr>
<tr>
<td>Diabetes 2%</td>
</tr>
</tbody>
</table>

18m lives lost globally to CVD\(^2\)

After years of decline, number of lives lost is on the rise again\(^3\)

~60m patients with ASCVD in US and EU5\(^4\)

Global CVD costs to surpass 1 trillion p.a. by 2025\(^1\)

<table>
<thead>
<tr>
<th>USD billion</th>
</tr>
</thead>
<tbody>
<tr>
<td>860</td>
</tr>
<tr>
<td>910</td>
</tr>
<tr>
<td>960</td>
</tr>
<tr>
<td>1000</td>
</tr>
<tr>
<td>1,100</td>
</tr>
</tbody>
</table>

2010 2015 2020 2025 2030

Recurrent heart attacks, strokes and death drive healthcare costs (55%) and result in productivity loss (45%)\(^1\)

Total cost 2010-2030 = USD 20 trillion

---

50 years of evidence demonstrate that effective and sustained LDL-C reduction improves cardiovascular outcomes*1,2

Log-linear association per unit change in LDL-C and the risk of cardiovascular disease5

Each mmol/L reduction in LDL-C reduces the relative risk of ASCVD events by 20% after 3 years and 1.5% in each subsequent year3

Relationship between LDL-C and MACE is supported by clinical trials involving ~500k patients3,4

Relation between LDL-C and outcomes is well established

---

Guideline evolution recognizes evidence of link between lower LDL-C and improved outcomes \(^3\)

### AHA/ACC (2018)\(^1\)

<table>
<thead>
<tr>
<th>Clinical ASCVD</th>
<th>Very high CVD risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C reduction by ≥50%</td>
<td>LDL-C reduction to &lt;70 mg/dL (1.8 mmol/L)</td>
</tr>
</tbody>
</table>

### ESC/EAS (2021)\(^2\)

<table>
<thead>
<tr>
<th>High CV risk</th>
<th>Very high CV risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C reduction to &lt;70 mg/dL (1.8 mmol/L) and LDL-C reduction by ≥50%</td>
<td>LDL-C reduction to &lt;55 mg/dL (1.4 mmol/L) and LDL-C reduction by ≥50%</td>
</tr>
</tbody>
</table>

Leqvio® delivers effective and sustained\textsuperscript{3} LDL-C reduction of up to 52%\textsuperscript{1,2} with twice-yearly\textsuperscript{4} HCP-administered dosing

Leqvio® effected significant reductions in LDL-C vs. placebo at Day 510, on top of SoC

Range, -47.9% - 52.3%

<table>
<thead>
<tr>
<th>Study</th>
<th>Between group difference</th>
<th>Between group difference (in absolute values)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORION-11\textsuperscript{1}</td>
<td>-49.9% (P&lt;0.0001)</td>
<td>-49.7 mg/dL (P&lt;0.0001)</td>
</tr>
<tr>
<td>ORION-10\textsuperscript{1}</td>
<td>-52.3% (P&lt;0.0001)</td>
<td>-56.8 mg/dL (P&lt;0.0001)</td>
</tr>
<tr>
<td>ORION-9\textsuperscript{2}</td>
<td>-47.9% (P&lt;0.0001)</td>
<td>-69.6 mg/dL (P&lt;0.0001)</td>
</tr>
</tbody>
</table>

LDL-C – Low Density Lipoprotein Cholesterol. ASCVD – Atherosclerotic Cardiovascular Disease. 1. Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol: Kausik K. Ray, M.D., M.Phil., R. Scott Wright, M.D., David Kallend, M.D., Wolfgang Koenig, M.D., Lawrence A. Letter, M.D., Frederick J. Raal, Ph.D., Jenna A. Blitch, B.A., Tara Richardson, B.A., Mark Jaros, Ph.D., Peter L.J. Wijngaard, Ph.D., and John J.P. Kastelein, M.D., Ph.D., for the ORION-10 and ORION-11 Investigators*: March 18, 2020, at NEJM.org. DOI: 10.1056/NEJMoa1912387. 2. Inclisiran for the Treatment of Heterozygous Familial Hypercholesterolemia: Frederick J. Raal, M.D., Ph.D., David Kallend, M.B., B.S., Kausik K. Ray, M.D., M.Phil., Traci Turner, M.D., Ph.D., for the ORION-9 Investigators*: March 18, 2020, at NEJM.org. DOI: 10.1056/NEJMoa1913805. 3. Across the 6-month dosing interval. Note: Leqvio® is approved in Europe; in the US Leqvio® has investigational status. 4. After an initial dose, again at 3 months, and again every six months thereafter. As a strong complement to a maximally tolerated statin.
In the US, Leqvio® is positioned to meet the needs of 80% of statin-treated ASCVD patients currently not at LDL-C goal

US ASCVD patient population

| Diagnosed | 30m |
| Statin treated | 20m |
| At LDL-C goal | 4m |
| Non-statin therapy | 1m |

Leqvio® is uniquely positioned to address unmet needs in ASCVD

- **A1** Adherence
  - Effective and sustained LDL-C reduction with two doses per year, generally well-tolerated

- **A2** Access
  - Medical benefit coverage for majority of patients at launch

- **A3** Affordability
  - 0 USD expected co-pay for 2/3 patients at launch

Inclisiran approved in 50 countries; US PDUFA date January 1, 2022

USA
- FDA review ongoing with PDUFA goal date Jan 1, 2022
- Launch preparation ongoing to enable readiness of health systems, drive awareness and facilitate access

Ex-US
- Approved in 50 countries
  - 30 EU/EEA countries and other countries including UK, Canada, Australia, and Switzerland
  - Launched in more than 10 countries
  - Reimbursement reviews ongoing
- Regulatory reviews ongoing in more than 20 countries
Large integrated program to establish Leqvio® as the standard of care in ASCVD management

<table>
<thead>
<tr>
<th>Lipid lowering</th>
<th>Outcomes</th>
<th>Healthcare system partnerships</th>
<th>Implementation science and RWE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Registration trials</td>
<td>Secondary Prevention</td>
<td>NHS collaboration</td>
<td>Initiation of treatment</td>
</tr>
<tr>
<td>ORION-3 (Ph2 extension)</td>
<td>ORION-4 (Oxford)</td>
<td>VICTORION-SPRIT (UK)</td>
<td>VICTORION-INITIATE (US)</td>
</tr>
<tr>
<td>ORION-5 (Ph3 HoFH)</td>
<td>VICTORION-2-PREVENT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORION-8 (Ph3 extension)</td>
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</table>

Geographic expansion

<table>
<thead>
<tr>
<th>ORION-14 (China)</th>
<th>ORION-17 (Oxford)</th>
<th>Post-ACS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORION-18 (China)</td>
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<td></td>
</tr>
<tr>
<td>ORION-15 (Japan)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Diverse patient populations

<table>
<thead>
<tr>
<th>ORION-13 (V-YOUTH)</th>
<th>VICTORION-INCEPTION (US)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORION-16 (V-YOUTH)</td>
<td></td>
</tr>
</tbody>
</table>

>75,000 patients in >50 countries; program expansion underway
Long-term investment to confirm benefit of Leqvio® on cardiovascular outcomes

### Market potential

<table>
<thead>
<tr>
<th>Indication</th>
<th>Asset potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlipidemia³</td>
<td>&lt;USD 1bn</td>
</tr>
<tr>
<td>Secondary prevention (CVRR)</td>
<td></td>
</tr>
<tr>
<td>Primary prevention (CVRR)</td>
<td></td>
</tr>
</tbody>
</table>

Long-term program involving ~70,000 patients across ~50 countries

#### ORION-4¹

**Secondary prevention**
- Evaluate impact of treatment with inclisiran on MACE
- Patients with established ASCVD
- N = 15,000
- Countries: UK, US
- Conducted in collaboration with Oxford University
- Status: Ongoing
- Estimated completion: 2026

#### VICTORION-2-PREVENT²

**Secondary prevention**
- Evaluate impact of treatment with inclisiran on MACE and CV Death
- Patients with established ASCVD
- N = 15,000
- ~50 countries
- Status: Ongoing
- Estimated completion: 2028

#### ORION-17

**Primary prevention**
- Evaluate impact of treatment with inclisiran on MACE
- Subjects 55 years and older
- N = ~40,000
- Country: UK
- Conducted in collaboration with Oxford University
- Status: In planning
- Estimated completion: ~2030

1. ClinicalTrials.gov Identifier: NCT03705234.  
2. ClinicalTrials.gov Identifier: NCT05030428.  
3. Adult and pediatric hyperlipidemia.
Pelacarsen (TQJ230)

Antisense oligonucleotide for the reduction of lipoprotein(a)

Phase 3

Key highlights

- 1/5 people have elevated Lp(a) which increases cardiovascular risk ~2-fold
- No therapies available to lower Lp(a)
- Pelacarsen is expected to be the first disease modifying treatment for Lp(a) and expected to reduce CV risk
- Focus on population at highest risk of ASCVD (8m in G7) where pelacarsen has unique effect
- Ph2b data showed potent and consistent reduction of Lp(a) with excellent tolerability and safety
- Recruitment for Ph3 outcomes trial HORIZON extended to early 2022 due to COVID-19. Trial readout expected 2025
- US/EU: Patent on composition of matter (2034/2034)

CV – Cardiovascular      ASCVD – Atherosclerotic Cardiovascular Disease      1. Tsimikas S. J Am Coll Cardiol. 2017;69:692-711; Kamstrup PR et al. JAMA. 2009;301(22):2331-8; 2x fold increase if considering 50 mg/dL as high. 2. Potential patients defined by the population studied in Lp(a)HORIZON: patients with elevated Lp(a) and MI, stroke or PAD. Potentially eligible population dependent on trial results and label 3. Patent term extensions and regulatory-based exclusivities are possible
Lp(a) is an independent risk factor for ASCVD\(^1\) that cannot currently be treated

---

Lp(a) is an **independent**, inherited and causal risk factor for CVD, with elevated Lp(a) mediating MI, stroke, and PAD

Lp(a) consists of an **LDL-like particle** which is covalently bound to apo(a)

Lp(a) levels are primarily genetically determined and not influenced by diet or exercise

There are currently **no approved therapies** to treat elevated Lp(a)

---

ASCVD – Atherosclerotic Cardiovascular Disease. Lp(a) – Lipoprotein a. CVD – Cardiovascular Disease. LDL – Low Density Lipoprotein. MI – Myocardial Infarction. PAD – Peripheral Artery Disease. Apo(a) – Apolipoprotein(a). ApoB-100 – Apolipoprotein B-100. KIV – Kringle IV. Lp(a) figure adapted from Tsimikas S. J Am Coll Cardiol 2017;69:692–711. \(^1\) The effect of pelacarsen on cardiovascular morbidity and mortality is currently being studied in the HORIZON trials. Note: pelacarsen is an investigational product.
Elevated Lp(a) is highly prevalent and one of the strongest genetic CVD risk factors\(^1-6\)

1 in 5 people worldwide have elevated Lp(a)\(^1,2\)

1.4 billion people have elevated Lp(a)*, increasing their ASCVD risk\(^1,2\)

Lp(a) is both the most common monogenic CVD risk factor and one of the strongest genetic CVD risk factors\(^2-5\)

**Indication**  **Asset potential**
---
CVRR (Lp(a)) \(^7\)  |
- **<USD 1bn**
- **USD 1-2bn**
- **>USD 2bn**

The prevalence of elevated Lp(a)* varies by geography

North America 20% | 73m

Latin America 15% | 97m

Europe 20% | 148m

Asia 10% | 261m

Africa 30% | 376m

S. Asia 25% | 469m

Oceania 20% | 8m

---

Lp(a) – Lipoprotein a,  CVD – Cardiovascular Disease,  *Lp(a) >50 mg/dL or >125 nmol/L.
6. The effect of pelacarsen on cardiovascular morbidity and mortality is currently being studied in the HORIZON trial.
7. Secondary prevention  
Note: pelacarsen is an investigational product.
Elevated Lp(a) increases cardiovascular risk\(^5\) ~2-fold, a level similar to LDL-C

Lp(a) is an independent, genetic and causal risk factor for MI, stroke and PAD\(^{1,2,3}\)

- **Risk ratio (95% CI)**
- **Usual Lp(a), Geometric Mean, mg/dL**
  - 0.8
  - 1.0
  - 1.2
  - 1.4
  - 1.6
  - 1.8
- **Adjustment for age and sex only**
- **Non-fatal MI and coronary death (9318 cases)**

Elevated Lp(a) increases risk for CV-events ~2-fold\(^{1,3,4}\)

- **Lp(a) mg/dL**
  - >117
  - 77-117
  - 30-76
  - 5-29
  - <5
- **Multivariable and KIV\(_2\) adjusted**
- **Myocardial infarction (592 cases)**

---

CI – Confidence Interval. CV – Cardiovascular. KIV – Kringle IV. Lp(a) – Lipoprotein(a).

4. 2x fold increase if considering 50 mg/dL as high.
5. The effect of pelacarsen on cardiovascular morbidity and mortality is currently being studied in the HORIZON trial. Note: pelacarsen is an investigational product.
Pelacarsen: An innovative approach to reducing Lipoprotein(a)

Apolipoprotein(a) is required for the assembly of Lp(a)

Pelacarsen specifically targets Lp(a) production

- Enters hepatocytes through ASGPR
- Binds to apolipoprotein(a) mRNA
- Prevents apolipoprotein(a) synthesis
- Lowers levels of circulating Lp(a)
Pelacarsen is the only therapy that can lower Lp(a) below risk threshold\(^1\) compared to other approaches

**Comparison of Lp(a) lowering effect\(^2\)**

![Graph showing comparison of Lp(a) lowering effect](image)

Pelacarsen significantly reduced Lp(a) in CVD patients in Ph2b

Ph2b results – pelacarsen vs. placebo
NEJM Tsimikas, et al. 2020

Ph2b data showed:
- Lp(a) levels were reduced to ≤50mg/dL in 98% of CVD patients following treatment with pelacarsen 20mg once a week
  - Dose-dependent Lp(a) reductions up to 80%
- Good tolerability and safety profile
- 80mg monthly is being evaluated in Ph3

Pelacarsen significantly reduced Lp(a) in CVD patients in Ph2b

P-values represent comparison to pooled placebo

Lp(a) HERITAGE prevalence study found 21% of patients with Lp(a) with ≥ 70mg/dl (HORIZON cut off)

Prevalence study

- Study evaluated prevalence of elevated Lp(a) levels in patients with established CVD
- > 48,000 patients, > 900 sites across 48 countries
- Study initiated April 2019, completed July 2021
- Median Lp(a) levels observed were as expected

Number and percentage of subjects in specific Lp(a) categories

- ≥ 70 mg/dL: 21.1%
- ≥ 50 mg/dL: 28.8%
- ≥ 30 - < 50 mg/dL: 9.9%
- < 30 mg/dL: 61.3%


- Appendix
- Respiratory & Allergy
- Submission schedules
**Lp(a)HORIZON - Ph3 CV outcome study ongoing**

Readout expected in 2025

Randomized double-blind, parallel group, placebo-controlled, multicenter study to assess effect of TQJ230 on MACE in patients with established CV disease

**Study population**
Patients with established CV disease (prior MI, stroke, PAD) and Lp(a) ≥70mg/dL

**Objectives**
- Primary endpoint: Time to first occurrence of expanded MACE in the overall study population and in a subpopulation of patients with Lp(a) ≥90mg/dL both tested concurrently.
- Secondary endpoints include time to first occurrence of MACE, coronary events composite.

**Readout expected in 2025**

---

Urgency to test for Lp(a) is growing in guidelines

**NLA, AHA**

**Awareness** of the presence of elevated Lp(a) is important, because high Lp(a) increases atherosclerotic cardiovascular disease risk and could inform clinical decision-making regarding risk management.

**Lp(a) screening:** All adults with personal or family history of premature ASCVD, severe hypercholesterolemia, suspected FH

**Lp(a) threshold:** >50 mg/dL (>100nmol/L) for ASCVD

**Treatment:** Consider intensification of treatment of LDL and other risk factors

**ESC/ EAS**

**Lp(a) screening:** All adults once in a lifetime

**Lp(a) threshold:** None for ASCVD. Primary prevention patients with >180mg/dL (>430nmol/L) CV risk equivalent to HeFH

**Treatment:** Consider intensification of treatment of LDL and other risk factors


Pelacarsen is an investigational product.
**Iptacopan (LNP023)**

Oral Factor B inhibitor targeting the alternative complement pathway

**Phase 3**

**Key highlights**

- **Across nephrology and hematology**, the iptacopan development program covers indications with limited (PNH\(^1\), aHUS\(^2\), LN\(^3\), ITP\(^4\)) or no approved treatments (IgAN\(^5\), C3G\(^6\), CAD\(^7\), iMN\(^8\)).

- By inhibiting the complement pathway, iptacopan **addresses the underlying pathophysiology** of indications in scope with oral convenience, good safety and tolerability based on Ph2 data.

- In renal, iptacopan has **disease-modifying potential** and could delay the need for dialysis and/or transplant\(^9\).

- In PNH, iptacopan has 1L potential given it addresses both intra- and extravascular hemolysis.

- **Pipeline in a pill** with potential to deliver multi-blockbuster revenue.

- Positive Ph2 data in PNH, C3G and IgAN. **Ph3 data readouts in PNH (H2 2022), C3G (2023), and IgAN (2023)**\(^10\). First filings expected 2023.

- **US/EU**: Patent on compound (2034/2034)\(^11\).

---

1. PNH = paroxysmal nocturnal hemoglobinuria  
2. aHUS = atypical hemolytic uremic syndrome  
3. LN = Lupus nephritis  
4. ITP = Immune Thrombocytopenic Purpura  
5. IgAN = IgA nephropathy  
6. C3G = C3 glomerulopathy  
7. CAD = cold agglutinin disease  
8. iMN = idiopathic membranous nephropathy  
9. Orphan Drug Designations: C3G (US/EU), PNH (US/EU), IgAN (EU)  
10. 9 months readout may support US submission for conditional approval  
11. Patent term extensions and regulatory-based exclusivities are possible.
Pipeline in a pill with global multi-blockbuster potential across several nephrology and hematology diseases

<table>
<thead>
<tr>
<th>Market potential</th>
<th>Asset potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td></td>
</tr>
<tr>
<td>IgAN, C3G, aHUS, IMN, LN, PNH, ITP, CAD</td>
<td>☺☻☻☻☻</td>
</tr>
<tr>
<td>☺☻☻☻☻ &lt;USD 1bn</td>
<td>☻☻☺☺☺ USD 1-2bn</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Addressable patients</th>
<th>US prevalence thousands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td></td>
</tr>
<tr>
<td>PNH</td>
<td>&lt;10</td>
</tr>
<tr>
<td>C3G</td>
<td>&lt;10</td>
</tr>
<tr>
<td>aHUS</td>
<td>&lt;10</td>
</tr>
<tr>
<td>CAD</td>
<td>&lt;10</td>
</tr>
<tr>
<td>IgAN</td>
<td>~46-55</td>
</tr>
<tr>
<td>IMN</td>
<td>~80</td>
</tr>
<tr>
<td>LN</td>
<td>~100</td>
</tr>
<tr>
<td>ITP</td>
<td>~100</td>
</tr>
<tr>
<td>CAD</td>
<td>~100</td>
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</table>

<table>
<thead>
<tr>
<th>Indication</th>
<th>2021</th>
<th>2022</th>
<th>2023</th>
<th>2024</th>
<th>2025</th>
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<tbody>
<tr>
<td>IgAN</td>
<td>Ph3</td>
<td></td>
<td>★</td>
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<tr>
<td>C3G</td>
<td>Ph3</td>
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</tr>
<tr>
<td>aHUS</td>
<td>Ph3</td>
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<td>IMN</td>
<td>Ph2</td>
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<td>LN</td>
<td>Ph2</td>
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<tr>
<td>CAD</td>
<td>Ph2</td>
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</tbody>
</table>

* 9 months readout may support US submission for conditional approval

IgAN = IgA nephropathy. C3G = C3 glomerulopathy. aHUS = atypical hemolytic uremic syndrome. IMN = idiopathic membranous nephropathy. LN = lupus nephritis. PNH = paroxysmal nocturnal hemoglobinuria. ITP = Immune thrombocytopenic purpura. CAD = Cold agglutinin disease. 1. Estimated number of patients at high risk of progression with proteinuria >1g/day (~25%-30%). Ultra-Rare: < 10 thousand patients. 2. Across indications.
**Iptacopan selectively targets the alternate complement pathway leaving direct signaling through classical and lectin pathways intact**

The complement pathway plays a role in a range of rare kidney and hematological diseases.

**Iptacopan (LNP023)** is an oral, first-in-class, potent and selective small-molecule inhibitor of factor B (FB).

Iptacopan binds to FB to suppress the activity of C3 convertase and thus signaling from the alternative complement pathway (AP) and activation of the amplification loop.

This prevents downstream generation of the C5 convertase complex, opsonization, and formation of C3a and C5a anaphylatoxins and membrane attack complex (MAC).

Direct classical and lectin pathway signaling remains intact, resulting in a potentially lower meningococcal infection risk in vaccinated patients compared to terminal complement pathway inhibitors.

Iptacopan has the potential to be a first line oral anti-complement mono-therapy in patients with PNH

Hematological response to eculizumab

- Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, life-threatening blood disorder caused by an acquired mutation in hematopoietic stem cells that leads to absence of complement-regulatory proteins

**Prevalence:** WW 7-16 cases/million; US 5-6k

Many patients remain anemic and transfusion dependent despite eculizumab treatment

- C3-mediated extravascular hemolysis not addressed by anti-C5
- ~40% remain anemic (Hb <10g/dl) of which ~50% are transfusion dependent

By specifically targeting the complement pathway proximally, iptacopan could address both intra- and extravascular hemolysis and thereby address the remaining unmet need in PNH

Interim Ph2 data already showed that iptacopan provides clinical benefits as add-on to eculizumab in patients with residual hemolysis

---

2. Petropoulou AD 2010
3. Hb = Hemoglobin
Positive Ph2 study shows clinically meaningful increases in hemoglobin

Dose Cohort\(^1\): 50 → 200mg BID\(^3\)

1. One patient was excluded for Hb analyses due to an RBC transfusion that occurred between screening and baseline, raising Hb from 71 to 110 g/L.
2. MDS = Myelodysplastic syndrome.
3. BID = twice a day.

Data (anti-C5 naive) presented at EHA 2021

- **Primary endpoint** of reducing LDH\(^1\) levels by ≥60% at Week 12 met; LDH reduction was rapid and durable
- Patients experienced rapid, durable increase in hemoglobin
- All patients except one (blue line) remained transfusion-free until Week 12
  - This patient had pre-existing MDS\(^2\), requiring 13 RBC transfusions during the year prior to study entry

---

1. CI = confidence interval.
2. MDS = Myelodysplastic syndrome.
**APPLY-PNH Ph3 to show superiority of iptacopan vs. SoC Anti-C5**

**Population (n ~91)**
Adult PNH patients (Hb <10g/dL) on a stable regimen of anti-C5 therapy 6 months prior to randomization

**Primary endpoints**
Proportion of patients achieving increase in Hb ≥2g/dL from baseline in the absence of RBC^1 transfusion

Proportion of patients achieving Hb ≥12g/dL in the absence of RBC^1 transfusion

**Primary readout** expected in H2 2022

<table>
<thead>
<tr>
<th>Time</th>
<th>Anti-C5 antibody (n= 56)</th>
<th>LNP023 200mg BID^2 (n= 35)</th>
<th>Continue with LNP023 200mg BID^2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>Up to 8 weeks</td>
<td>24 weeks</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Study period</td>
<td>Screening period</td>
<td>Randomized treatment period</td>
<td>Treatment extension period</td>
</tr>
<tr>
<td>D-60</td>
<td>D1</td>
<td>D168</td>
<td>D336 EoS^3</td>
</tr>
</tbody>
</table>

1. RBC = Red Blood Cell.  2. BID = twice a day.  3. EoS = end of study.
Iptacopan has potential to be disease modifying, delaying or preventing need for dialysis and/or kidney transplant

K-M analysis of kidney survival\(^1\) by C3G subtype\(^4\)

- \(\text{C3G is an ultra-rare, severe form of primary glomerulonephritis and is commonly diagnosed in adolescents and young adults}\)
- \(\text{Prevalence: US: } \sim 10k; \text{ EU5: } \sim 1.5-2.5k; \text{ China: } \sim 32k; \text{ Japan: } \sim 3.2k\)
- \(\text{There are currently no approved therapies}\)
- \(\sim 50\% \text{ patients develop kidney failure within } 10 \text{ years of diagnosis}\)
- \(\text{Post-transplantation recurrence and allograft loss is common (50\% in } \text{DDD}, 75\% \text{ in } \text{C3GN})\)
- \(\text{Characterized by complement dysregulation and complement C3 deposition in the kidney}\)
- \(\text{In C3G, iptacopan has the potential to be disease modifying and to delay, or even prevent, the need for dialysis and/or transplant}\)

1. End-stage kidney disease (ESRD) free renal survival
2. Dense Deposit Disease
3. C3 glomerulonephritis
Ph2 showed clinically meaningful 45% reduction in proteinuria...

UPCR\(^3\) (24h urine collection) vs. baseline over time\(^1\)

<table>
<thead>
<tr>
<th>Time, days</th>
<th>UPCR 24h ratio to baseline (80% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.55 (0.46, 0.65) (P=0.0003)</td>
</tr>
</tbody>
</table>

1. Note: all patients from cohort A (with native kidney).
3. UPCR = Urine protein to creatinine ratio.

Primary endpoint data presented at ASN 2021

- Significant and clinically meaningful reduction in proteinuria of 45% from baseline
- Statistically significant reduction in C3 protein deposits observed in transplanted kidneys
- Favorable safety and tolerability profile
... with improvements in trajectory of renal function decline compared to historical patients’ trend

Mean eGFR\(^1\) slope and 95% CI\(^2\) indicated by bold blue line and surrounding shadowed area

Data presented at ERA-EDTA 2021

- Iptacopan treatment leads to stabilization of renal function already at 3 months
- Estimated effect corresponds to a mean predicted eGFR preservation of 6.4 mL/min/1.73m\(^2\) over 12 weeks (p=0.0459)

Individual patient eGFR slopes (n=12) for up to 2 years prior to and following commencement of 12-week course of iptacopan

1. eGFR = estimated glomerular filtration rate.  2. CI = confidence interval.
APPEAR-C3G Ph3 ongoing to support global regulatory submissions

**Population**
Adult patients with biopsy-confirmed C3G and native kidney. Proteinuria ≥1g/g (24h UPCR$^1$)

**Primary objectives**
Proteinuria reduction at 6 months

**Secondary objectives**
eGFR$^3$, proportion achieving a composite renal endpoint, reduction in glomerular inflammation, safety and tolerability

**Readout** expected in 2023

---

1. UPCR = urinary protein to creatinine ratio  
2. BID = twice a day  
3. eGFR = estimated glomerular filtration rate
Iptacopan could potentially delay the need for dialysis and/or transplant

**TA³-proteinuria: the strongest clinical predictor for IgAN kidney function decline²**

- **Most common primary glomerulonephritis**, most common cause of kidney failure in young adult Caucasians¹
- **Prevalence**: US: ~185k; EU5: ~32-51k; China: ~1m; Japan: ~130k
- **Standard of care (SoC)**: currently no approved therapies, focus on supportive care
- **Proteinuria ≥1g/day** is the strongest risk factor for poor prognosis in IgAN: ~30% of patients with proteinuria 1-2 g/day progress to kidney failure within 10 years
- **Proteinuria reduction** is an important clinical goal in IgAN and a relevant endpoint for accelerated registration pathways by FDA and other authorities
- **Activation of the alternative pathway (AP)** is present in almost 90% of biopsies
- By targeting the AP, iptacopan has the potential to slow disease progression and delay the need for dialysis and/or transplant

---

³ TA = time averaged.

---

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---
Ph2 showed 200mg BID\(^3\) led to a clinically meaningful proteinuria reduction of 23% at Day 90

![Estimated dose-response curve](image)

- **Primary endpoint data presented at ERA-EDTA 2021**
  - Statistically significant dose-response in proteinuria reduction\(^6\) versus placebo at 90 days
  - Iptacopan 200mg BID\(^3\) led to a 23% proteinuria reduction (80% CI: 8%, 34%)
  - Encouraging trend to early stabilization of renal function (eGFR\(^7\))
  - Favorable safety and tolerability profile; no serious infections
  - Further UPCR reduction at day 180 when compared to day 90

---

1. UPCR = Urine protein to creatinine ratio
2. Multiplicity-adjusted \(P\)-value, analysis adjusted for baseline UPCR (24-hour) and ancestry
3. BID = twice daily
4. MCP-mod = Multiple Comparison Procedure – Modelling
5. CI = confidence interval
6. MMRM = mixed model repeated measurements
7. eGFR = estimated glomerular filtration rate
8. 24-hour UPCR

---

\(\text{UPCR} = \) Urine protein to creatinine ratio
\(\text{MMRM} = \) mixed model repeated measurements
\(\text{eGFR} = \) estimated glomerular filtration rate

---

UPCR (24-hour urine collection) (g/mol) ratio to placebo (or ratio to baseline)

- MCP-mod\(^4\) estimates: \(0.99, 0.94, 0.87\)
- MMRM\(^6\) estimates: \(0.77, 0.77\)
- Pointwise 80% CI: \((0.66, 0.92), (0.66, 0.92)\)

---

1-sided **\(P=0.038\)**

23% reduction vs placebo
APPLAUSE-IgAN Ph3 study provides the basis for potential filing on proteinuria reduction (IA)

**Population**

Biopsy-confirmed IgAN patients at risk of progression with elevated proteinuria (UPCR$_2^2$ ≥1g/g) despite being on stable background therapy$^1$

**Primary objectives**

**IA:** Assess superiority of iptacopan vs. placebo in reduction of proteinuria$^2$ at 9 months; to support regulatory submission for accelerated/conditional approval

**EoS:** Assess superiority of iptacopan vs. placebo in slowing progression of IgAN measured by annualized total slope of eGFR decline over 24 months

**Readout** expected in 2023 (IA) and 2025 (EoS)

---

1. Including at least maximally tolerated dose of ACEI/ARB for at least 90 days.
2. UPCR (urine protein-to-creatinine ratio) from 24-h urine collection.
3. BID = twice daily.
Immunology, Hepatology & Dermatology
In IHD, we are deepening our presence in Rheumatology and Dermatology

IHD strategy

Focus on areas of highest need in rheumatology
- Deliver strong growth in SpA while capitalizing on LCM in areas of high unmet need
- Advance multiple assets in Sjögren’s and Lupus to provide value to patients, HCP and HCS: ianalumab, iscalimab, remibrutinib, MHV370
- Fast-forward in osteoarthritis with LNA043

Become #1 in immuno-dermatology
- Expand Cosentyx leadership in dermatology through LCM e.g., in Hidradenitis Suppurativa
- Establish global leadership in CSU with ligelizumab and remibrutinib
- Accelerate Atopic Dermatitis portfolio

Assets highlighted today:
- Cosentyx®, ligelizumab, remibrutinib, ianalumab, LNA043
- Ligelizumab, LNA043
- LNA043 (knee OA)
- DFV890 (OA)
- LRX712 (OA)
- Remibrutinib (SJS)
- MHV370 (SJS, SLE)
- NGI226 (Tendinopathy)
- Cosentyx® (HS)
- Ligelizumab (CSU)
- Ligelizumab (ClindU)
- Remibrutinib (CSU)
- Cosentyx® (LP)
- Iscalimab (HS)
- LYS006 (Acne)
- LYS006 (HS)
- CMK389 (AD)
- LJN452 (NASH)
- ianalumab (AIH)
- ADPT02 (NASH)
- FIA586 (NASH)

AD: Atopic dermatitis; AIH: Autoimmune Hepatitis; axSpA: axial Spondyloarthritis; ClindU: Chronic Induced Urticaria; CSU: Chronic Spontaneous Urticaria; ERA: Enthesitis related Arthritis; GCA: Giant Cell Arteritis; HS: Hidradenitis Suppurativa; IV PsA/axSpA: PsA and axSpA intravenous regimen; JPsA: Juvenile Psoriatic Arthritis; LN: Lupus Nephritis; LP: Lichen Planus; NASH: Non Alcoholic Steato-Hepatitis; OA: Osteoarthritis; PsA: Psoriatic Arthritis; SJS: Sjögren’s Syndrome; SLE: Systemic Lupus Erythematosus; Tx: Transplant

Note: bars in Gantt chart indicate current phase of development.
**Cosentyx®** *(secukinumab)*

Fully human interleukin-17 inhibitor for psoriasis, psoriatic arthritis and axial spondyloarthritis

Marketed; LCM in Phase 2, 3

---

**Key highlights**

- Proven efficacy with **strong evidence in skin and joints**, >6 years of real-world experience, **reaching >500k patients** across 4 anchor indications (PsO, PsA, AS, nr-axSpA)

- LCM leading up to a **potential 10+ total indications** in areas of high unmet need (HS, LP, GCA, LN, JPsA and ERA), raising the **total addressable population to 10m patients**

- HS next growth opportunity. Ph3 studies met primary endpoint. Filing planned for 2022

- 3+ potential **formulation and dosing enhancements** with IV, 300mg autoinjector, PsO flexible dosing. IV submission in 2022

- **Peak sales expectations at least USD 7bn** driven by greater use of biologics, growth in China and comprehensive LCM

- **US/EU**: Patents on composition of matter and use (2029-2033/2030-2031)¹

---

¹. Includes extended patent terms. For additional information, please refer to the Novartis 20F 2020.
100+ trials reinforcing Cosentyx® comprehensive efficacy and consistent safety across all key facets of PsO, PsA and axSpA
Developing Cosentyx® into a total of 10+ indications and adding multiple label enhancements – peak sales potential at least USD 7bn

### Indication
- **Hidradenitis Suppurativa (HS)**
- **Lichen Planus (LP)**
- **Juvenile Psoriatic Arthritis (JPsA) & Enthesitis Related Arthritis (ERA)**
- **Giant Cell Arteritis (GCA)**
- **Lupus Nephritis (LN)**

#### Asset potential
- ○○○ USD 1bn
- ●●○ USD 1-2bn
- ○○○ ○○○ USD 2bn

### Indicated population
1. **HS**
   - >400K
   - Debilitating skin disease with significant QoL impact
2. **LP**
   - >2,500K
   - Inflammatory skin disease with impaired QoL
3. **JPsA & ERA**
   - >15K
   - Progressive, chronic pediatric diseases
4. **GCA**
   - >480K
   - Eye-sight threatening vasculitis in elderly
5. **LN**
   - >130K
   - Major cause of morbidity and mortality in SLE patients

---

**SLE – Systemic Lupus Erythematosus**

1. Total diagnosed population – not accounting for potential restrictions in label/treatment guidelines.
Hidradenitis Suppurativa
Secukinumab: potential novel therapy to address a debilitating disease

High unmet need in Hidradenitis Suppurativa

- Inflammatory skin disease of the folliculopilosebaceous unit
  - Intertriginous skin areas of the axillary, groin, perianal, perineal, and inframammary regions
  - Recurrent, painful nodules and abscesses, scarring, purulent discharge, odor and loss of function
- Prevalence ~1%, ~400k patients (200k in the US, 200k in EU5) with moderate to severe HS
- Under-diagnosed: diagnosis rate ~20%
- Available treatment options do not adequately reduce disease activity or prevent disease progression

Images reproduced with permission from Kang et al.²

### Ph3 program in Hidradenitis Suppurativa

#### SUNRISE & SUNSHINE

- Two identical randomized, double-blind, placebo-controlled, multicenter studies
- Moderate to severe HS patients with or without prior biologic exposure
- Efficacy and safety
- The primary endpoint is the HiSCR at Week 16
  - HiSCR response: ≥50% decrease in Abscess and Inflammatory Nodule count with no increase in the number of draining fistulae

#### Primary endpoint, safety

- Primary efficacy endpoint of HiSCR at Week 16 was met in both studies
- Safety data consistent with well established safety profile of Cosentyx
- Study remains blinded and data will be presented after week 52

---

3. AN: abscesses and inflammatory nodules count
Lichen Planus
Impaired quality of life without approved systemic therapies

Unmet need in Lichen Planus

- Chronic inflammatory disorder of the skin, oral cavity, genitalia, scalp, nails, or esophagus
- Prevalence: 0.4% - 2.6%\(^1\)
- Pruritic and painful
- Impact on quality of life comparable to psoriasis
- Current standard of care topical and systemic corticosteroids
  - Many patients refractory to SoC

Th17-driven disorder\(^2\)

Ex vivo scientific evidence

- Targeting of IL-17 pathway leads to a reduction of immune cell infiltrate in LP skin biopsies\(^2\)

Secukinumab case reports

- Clinical improvement of skin and mucosal lesions within 12 weeks of treatment\(^2,3,4\)

Secukinumab Ph2 in Lichen Planus

PRELUDE

- **Randomized, placebo-controlled, double-blind, multi-center trial**
- **Innovative basket study design evaluating 3 subtypes of lichen planus**
- **Primary endpoint:** Investigator’s Global Assessment (IGA) score less or equal 2 (IGA ≤2) at Week 16
- **Data expected H1 2022**

**Primary endpoint: IGA ≤2 at W16**

- **Mucosal LP**
  - Secukinumab 300mg Q4W (24 pts)
  - Placebo (12 pts)
  - Secukinumab 300mg Q2W
  - Secukinumab 300mg Q4W

- **Cutaneous LP**
  - Secukinumab 300mg Q4W (24 pts)
  - Placebo (12 pts)
  - Secukinumab 300mg Q2W
  - Secukinumab 300mg Q4W

- **L. planopilaris**
  - Secukinumab 300mg Q4W (24 pts)
  - Placebo (12 pts)
  - Secukinumab 300mg Q2W
  - Secukinumab 300mg Q4W

---

Giant Cell Arteritis (GCA)
Vision threatening large vessel inflammatory rheumatic disorder

Unmet need in GCA

- Adult primary systemic large vessel vasculitis
- Elderly patients (mean age, 74 years)
- Lifetime risk of disease: 0.5-1%\(^1\)
- Substantial morbidity due to irreversible vision loss, stroke\(^2\) and toxicity of prolonged glucocorticoid treatment
- An unmet medical need remains for safe and effective steroid sparing treatments
- Standard of Care: high dose systemic steroids, MTX or tocilizumab\(^3\)

Secukinumab Ph2 study demonstrates sustained efficacy in Giant Cell Arteritis; met all primary and secondary endpoints

GCA Ph2 TiTAIN study¹ results

Primary endpoint: Proportion of patients in sustained remission until Week 28²

<table>
<thead>
<tr>
<th></th>
<th>Median percent of patients with sustained remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secukinumab (N = 27)</td>
<td>70.1%</td>
</tr>
<tr>
<td>Placebo (N = 25)</td>
<td>20.3%</td>
</tr>
</tbody>
</table>

GCA, giant cell arteritis; N, number of patients in each treatment group, full analysis set

ClinicalTrials.gov identifier: NCT04930094. ¹. ACR Convergence 2021 Late-Breaking Abstracts. ². Sustained remission is defined as being without a flare and in adherence to the protocol prednisolone taper regimen. A flare is defined as recurrence of signs and symptoms after remission and/or ESR ≥ 30 mm/h and/or CRP ≥ 10 mg/L attributable to GCA as per investigator’s judgment. ³. Flares may occur during or after the steroid taper.
Secukinumab Ph3 program enrolled first patient in Oct 2021

**GCA Ph3 study design**

- Efficacy and safety of secukinumab versus placebo, in combination with glucocorticoid taper regimen, in patients with Giant Cell Arteritis (GCA): faster glucocorticoid taper on secukinumab arm
- Primary endpoint: sustained remission at week 52
- First patient enrolled in October 2021
- Estimated primary completion 2024

---

1. ClinicalTrials.gov identifier: NCT04930094
**IV regimen in Psoriatic Arthritis (PsA) and axial Spondyloarthritis (axSpA) with possible extension to other indications**

---

**A novel option for patients and HCPs**

**Unmet need in Psoriatic Arthritis (PsA) and axial Spondyloarthritis (axSpA) patients**

IV regimen provides additional options

- Weight-based dosing
- Needle-phobic patients
- Patients with a preference for physician administration

Potential to expand patient access to treatment

- First IL-17i available in an IV formulation
- Of current PsA/axSpA patients on biologic treatment, ~20% receive IV biologic

**Scientific rationale for IV formulation**

- Proven efficacy with s.c. dosing in axSpA and PsA
- Foundational IV safety dataset for future LCM indications
- Assessment of novel digital endpoints incl. sleep and activity

---

1. Source: US claims data and Novartis internal assumptions
Secukinumab IV efficacious in Psoriatic Arthritis (PsA) Ph3

INVIGORATE-2 Ph3 PsA IV study design

- Efficacy and safety of intravenous secukinumab up to 52 weeks in subjects with active Psoriatic Arthritis\(^1\)
  - Secukinumab 6mg/kg followed by 3mg/kg IV (N=191)
  - Placebo (N=190)
- Primary endpoint: ACR50 vs placebo at week 16

INVIGORATE-2 IV study results

- Demographics and baseline characteristics well balanced between treatment groups
- Primary and secondary efficacy endpoints
  - Statistically significant superiority of secukinumab IV compared to placebo
- Safety profile in line with well established safety profile of secukinumab

1. ClinicalTrials.gov Identifier: NCT04209205.  2. ACR50 (American College of Rheumatology 50) - is ≥ 50% improvement in measure of change in rheumatoid arthritis symptoms.
### Ligelizumab (QGE031)

Humanized anti-IgE monoclonal antibody blocking IgE/FcεRI pathway

#### Phase 3

**Key highlights**

- **~740k CSU patients inadequately controlled** on antihistamines in G6
  - Ligelizumab targets IgE/FcεRI pathway with potential to **become new standard of care** based on higher selectivity and different binding site than Xolair®
  - Ph2b showed higher efficacy compared to Xolair® and a clear dose-response. Results from Ph2b study in adolescent patients consistent with adult data
  - **Ph3 superiority studies vs. current SoC Xolair®** underway (PEARL 1, 2); results expected Q4 2021 with submission in 2022
  - **Initiating Ph3 studies** in CINDU and Food Allergy in Q4 2021
  - **US/EU**: anticipated regulatory-based exclusivity from regulatory approval (12 years/10 years)

---

1. G6 = US+EU
“CSU does not kill you, but it also does not let you live”*

CSU consists of unpredictable onset itch, hives and angioedema which greatly diminish QoL

Almost half of people with moderate-to severe chronic urticaria suffer from painful angioedema¹

Up to 1 in 3 people with moderate to severe chronic urticaria have depression or anxiety²

Patients report sleep as one of the worse affected aspects of their life³

About 1 in 5 patients report having to take time away from work due to their CSU³

Treatment gap:
Untapped opportunity with low biologic penetration at 13%

2.1 million treated CSU patients in G6 countries in 2021⁴

Treatment gap:
Patients inadequately controlled, not receiving biologic

Only ~13% of eligible patients are on biologic treatment

Patients controlled with up to 4-fold second generation antihistamines


1.3m

2.1m

~740k

110k

82
Ligelizumab best-in-disease potential driven by the IgE-FcεRI

AEC, airway epithelial cell; APC, antigen presenting cell; CSU, chronic spontaneous urticaria; FcεRI, high affinity IgE receptor; IgE, immunoglobulin E. Eggel A and Bern U. European Academy of Allergy and Clinical Immunology symposium, June 6-8, 2020, Digital congress.
**Chronic Spontaneous Urticaria**

In Ph2b, ligelizumab showed better symptom control compared to Xolair®

---

**Ph2b study with clear dose-response on complete hives control and UAS7\(^1\) change from baseline\(^2\)**

**A. Dose-response curve**

**B. Change from baseline in UAS7 over time**

---

1. UAS7 = Urticaria Activity Score over 7 days.
3. HSS7 = Hives Severity Score over 7 days.
**Ligelizumab Ph3 CSU studies**

Aim to demonstrate superiority vs Xolair®

---

**PEARL 1 and 2 results expected Q4 2021**

A press release will include the combined top line results of PEARL 1 and 2

1. **UAS7** = Urticaria Activity Score over 7 days.
2. Measured as DLQI = 0-1

**1º endpoint:**

- UAS7 at week 12

**2º endpoints at week 12:**

- % of subjects with no itch, no hives
- Improvement of itch severity score
- No impact on subject's quality of life
- Cumulative number of weeks without angioedema

**Expected submission:** 2022

---

**Head-to-head comparison vs SoC**

(highest approved Xolair® dose 300mg)

1. **UAS7** at week 12

---

2 multi-center, randomized, double-blind, active/placebo-controlled studies; recruited 2,059 adults and 93 adolescents

---

1. UAS7 = Urticaria Activity Score over 7 days.
2. Measured as DLQI = 0-1
Exploring ligelizumab in other IgE/FcεRI mediated diseases – Chronic Inducible Urticaria (CINDU)

IgE/FcεRI inhibition a promising therapeutic target in CINDU²

- ~1/3 of chronic urticaria patients have CINDU¹
- SoC is antihistamines²
- Disease triggers often unavoidable
- No approved therapies for uncontrolled CINDU patients²
- Therapeutic goal: complete symptom control²

**Ligelizumab Ph3 CINDU study**

Aim to investigate efficacy and safety in treatment of CINDU in adolescents and adults

---

**Pearl-Provoke Study attributes**

- A randomized, double-blind, placebo-controlled study
- Ph3 ongoing
- IgE inhibition effective in CINDU patients inadequately controlled with H1-antihistamines

Basket study design:

- 3 most common CINDU subtypes (N=348)

Submission planned 2025

---

CINDU = Chronic Inducible Urticaria

1. ClinicalTrials.gov Identifier: NCT05034058
Potential best-in-class therapy in Food Allergy

Protecting patients from reactions triggered by accidental exposure

- Prevalence: 3-8%
  - Allergy to multiple foods common
  - 73% include peanut allergy
- 42% of children and 51% of adults with ≥ one convincing food allergies have experienced ≥ one severe food-allergic reaction
- Reactions can be triggered by tiny exposures (e.g., fraction of a peanut)
- Current standard of care:
  - Allergen avoidance and epinephrine

High unmet need for effective and safe treatments to improve quality of life of patients and families

---


*Amended in May 2022
Ligelizumab Ph3 Food Allergy study
Aim to decrease reactivity to peanuts in patients with peanut allergy

Peanut1: Study to start Q4 2021

A 52-week, multi-center, randomized, double-blind placebo-controlled study to assess the efficacy and safety of ligelizumab in decreasing the reactivity to peanuts in patients with peanut allergy

- Primary endpoint: Proportion of participants who can tolerate a single dose of ≥ 600mg (1044mg cumulative tolerated dose) of peanut protein without dose-limiting symptoms at Week 12

Study attributes

- Food allergy sensitive to IgE interacting with its high affinity receptor (FcεRI)2
- Peanut allergy study spearheading other food allergy studies
- IgE blockade effective in several studies 3-5
- First submissions planned 2025

---

Developing ligelizumab in IgE/FcεRI pathway mediated diseases

### Market potential

<table>
<thead>
<tr>
<th>Indication</th>
<th>Asset potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSU</td>
<td></td>
</tr>
<tr>
<td>Food Allergy</td>
<td><img src="chart" alt="Asset potential" /></td>
</tr>
<tr>
<td>CINDU</td>
<td></td>
</tr>
</tbody>
</table>

- ![Asset potential](chart)
- USD 1bn
- USD 1-2bn
- >USD 2bn

### Addressable patients

<table>
<thead>
<tr>
<th>Indication</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSU</td>
<td>~740k</td>
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<tr>
<td>Food Allergy</td>
<td>3.40m</td>
</tr>
<tr>
<td>CINDU</td>
<td>300k</td>
</tr>
</tbody>
</table>

1. Approximate figures; Source: Novartis internal forecast for G6 countries

### Upcoming milestones for development program

<table>
<thead>
<tr>
<th></th>
<th>2020</th>
<th>2021</th>
<th>2022</th>
<th>2023</th>
<th>2024</th>
<th>2025</th>
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<tbody>
<tr>
<td>CSU</td>
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<td>Ph3</td>
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<tr>
<td>Food Allergy</td>
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<td>Ph3</td>
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<td>CINDU</td>
<td></td>
<td></td>
<td>Ph3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- CSU PEARLs readout in Q4 2021; submission 2022
- Food Allergy: Initiation of Ph3 program in Q4 2021
- CINDU: Ph3 ongoing
Key highlights

- **Remibrutinib (LOU064)**

  Oral, covalent BTK inhibitor targeting immune cell signaling

  Phase 3

  - **~740k CSU patients** inadequately controlled on antihistamines in G6\(^1\). Biologic penetration only 13%
  - **Remibrutinib** is a highly selective, potent covalent BTK inhibitor with potential for **best-in-class efficacy and safety**
  - Significant opportunity as **first option post H1-antihistamines** with oral convenience
  - Ph2b showed **rapid and biologic-like efficacy** and favorable benefit/risk profile across entire dose range tested. **No clinically relevant AEs** associated with BTK class\(^2\)
  - On track as **first to market BTKi in CSU** with Ph3 enrollment ongoing, submission expected 2024
  - **Direct-to-Ph3 initiated in RMS**. Exploring multiple other indications
  - **US/EU**: Patent on compound (2034/2034)\(^3\)

---

1. G6 = US/EU, CSU: Chronic Spontaneous Urticaria  
2. e.g., infections, cytopenias, bleeding, hepatic events  
3. Patent term extensions and regulatory-based exclusivities are possible
Remibrutinib: A highly selective and potent oral BTK inhibitor with best-in-class potential

BTK inhibition

- Targeting immune cell signaling through FcεR, FcγR and BCR
- BTK selectively expressed in cells of adaptive and innate immune system including B cells, macrophages, mast cells and basophils
- **Novartis BTKi** remibrutinib (LOU064) differentiated by high kinase selectivity combined with potent covalent BTK inhibition
- No significant off target toxicity observed in clinical trials to date
Favorable benefit/risk profile across the entire dose range, with no dose-dependent pattern of AEs

More patients achieved complete control (UAS7=0)

<table>
<thead>
<tr>
<th>Time (Weeks)</th>
<th>Response rate % (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.03</td>
</tr>
<tr>
<td>1</td>
<td>0.05</td>
</tr>
<tr>
<td>2</td>
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<td>3</td>
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<td>11</td>
<td>0.25</td>
</tr>
<tr>
<td>12</td>
<td>0.27</td>
</tr>
</tbody>
</table>

- More patients on remibrutinib achieved complete control, i.e. complete absence of hives and itch (UAS7=0) over 12-week treatment period
- High response rate maintained, up to end of treatment

Remibrutinib demonstrated good tolerability across the entire dose range tested with no safety signals

Key safety data include:

- No dose dependent increase of, treatment interruption or discontinuation due to LFT elevations
- No dose dependent cytopenias, treatment interruption or discontinuation due to low blood cell counts
- No clinically relevant adverse events associated with BTK inhibitor class (e.g., infections, cytopenias, bleeding, hepatic events) across the dose range tested

First oral therapy to advance to Ph3 in CSU in 2021 in H1 antihistamines inadequate responders. Best-in-class profile based on positive benefit/risk profile. Ph3 in CSU ongoing

AE – Adverse events CSU – chronic spontaneous urticaria UAS7 – weekly Urticaria Activity Score b.i.d. – two times a day.
Remibrutinib CSU Ph3 program started in November 2021

Positive results from Ph3 studies REMIX-1 and REMIX-2 will enable submission of remibrutinib in CSU as first-in-indication BTK inhibitor in 2024

Multicenter, randomized, double-blind, placebo-controlled studies in patients with CSU inadequately controlled by H1-AHs

Co-primary endpoints (PE\(^2\) @ week 12)
- Change from baseline in UAS\(^7\)
- Absolute change from baseline in ISS\(^7\) and HSS\(^7\)

Secondary endpoints (@ week 12)
- Disease activity control (UAS\(^7\) ≤6)
- Complete absence of hives and itch (UAS\(^7\) = 0)
- Reduction in ISS\(^7\) and HSS\(^7\) scores
- Achievement of DLQI = 0-1
- Sustained disease activity control
- Weeks without angioedema
- Safety and tolerability of remibrutinib (56 weeks)

ClinicalTrials.gov Identifier: NCT05030311/NCT05032157.
1. PA: Primary analysis.
2. PE: Primary endpoint.
3. UAS\(^7\) = weekly Urticaria Activity Score.
4. ISS\(^7\) = weekly Itch Severity Score.
5. HSS\(^7\) = weekly Hives Severity Score.
Remibrutinib is key to unlock full potential of CSU market, leveraging portfolio with ligelizumab

**Current SoC for patients uncontrolled on antihistamines**
- Lower mean weekly itch severity vs. placebo
- More patients with complete control vs. placebo

**Ligelizumab**
- Potential to become new biologic SoC
  - More patients with complete control than Xolair®
  - More convenient 1 injection per month

**Remibrutinib**
- Potential first option after antihistamines with oral convenience
  - Biologic-like efficacy
  - Favorable benefit/risk profile
  - No clinically relevant AEs associated with BTK class
  - Oral convenience
  - Only BTK in Ph3 in CSU

---

2014

2023

2025
Remibrutinib has significant commercial potential across indications

### Market potential

<table>
<thead>
<tr>
<th>Indication</th>
<th>Prevalence</th>
<th>Asset potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSU</td>
<td>~740k</td>
<td>USD 1bn, 1-2bn</td>
</tr>
<tr>
<td>RMS</td>
<td>&gt; 0.5m</td>
<td>&gt;USD 2bn</td>
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</table>

### Upcoming milestones for development program

<table>
<thead>
<tr>
<th>Indication</th>
<th>Year</th>
<th>Milestone</th>
</tr>
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<tbody>
<tr>
<td>CSU Ph2b</td>
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<td>Ph2b</td>
</tr>
<tr>
<td>CSU Ph3</td>
<td></td>
<td>REMIX-1 and REMIX-2</td>
</tr>
<tr>
<td>MS Ph3</td>
<td></td>
<td>REMODEL-1 and REMODEL-2</td>
</tr>
</tbody>
</table>

REMIX-1 and REMIX-2
- Enrollment started November 2021
- Submission in 2024

REMODEL-1 and REMODEL-2
- Enrollment start December 2021
- Submission in 2025

---

1. G6 = US+EU5.  CSU: Chronic Spontaneous Urticaria, MS: Multiple Sclerosis.
**lanalumab**
(VAY736)

Fully human monoclonal antibody binding to and blocking the function of the BAFF receptor

**Phase 2**

**Key highlights**

- **400k patients** with moderate to severe Sjögren’s disease in G7
- **No disease-modifying treatment** available, systemic features in 40% patients, 5% develop Non-Hodgkin lymphoma
- Dual MoA expected to deliver **deeper, longer-term disease remissions** vs other B-cell depleting agents
- Potential to become **first disease modifying therapy** in Sjögren’s based on **positive Ph2b** showing dose response and good tolerability. Filing expected in ≥2026
- Investigating lanalumab in **additional prototypical B cell associated diseases** including LN (Ph3 expected to start in 2022), SLE (Ph2a), autoimmune hepatitis (Ph2b), CLL (Ph1/2a)
- **US/EU**: Anticipated regulatory-based exclusivity from regulatory approval (12 years/10 years)
Ianalumab (VAY736) has unique dual MoA: Blocking BAFF-R and depleting B cells

**BAFF:BAFF-R signaling blockade**

- **BAFF**
  - Differentiation
  - Proliferation
  - Survival

- **BAFF-R**
  - Check point
  - B cell

**VAY736**

**Enhanced* ADCC-mediated B cell depletion**

- **Tissue - peripheral B cell re-circulation**
- **Peripheral blood**
  - B cells

**Plasmablast**

- B cell proliferation
- Hyper-IgM globulinemia
- Auto-Ab production

**Plasma cell**

*afucosylated Fc

**Dual MoA and more profound B cell depletion expected to deliver deeper, longer term disease remissions vs other B-cell depleting agents**

ADCC = Antibody-dependent cellular cytotoxicity
Sjögren’s syndrome and rationale to target BAFF-R with ianalumab

Prevalence and treatment
- Prevalence 0.2%
  - Systemic features in 40%
  - 5% develop Non-Hodgkin lymphoma
- No disease modifying treatment

Rationale for ianalumab
- Hallmark diagnostic features:
  - B-cell hyperreactivity and autoantibodies
  - Autoimmune inflammatory infiltrate including BAFF-R+ B cells in exocrine glands (salivary and tear glands show ectopic lymphoid structures)
- Depleting B-cells and blocking BAFF-R targets underlying disease mechanism

Ph2b study in Sjögren’s disease: Efficacy on systemic disease manifestations

Randomized, double-blind, placebo-controlled, multicenter studies to evaluate the dose response on efficacy and safety of ianalumab, q4wk

Study attributes

- Primary endpoint was met; dose response of ianalumab defined as change in ESSDAI from baseline at 24 weeks
- Efficacy demonstrated on systemic extra-glandular manifestations of Sjögren’s disease
- Secondary endpoint of ESSPRI not achieved
- Good tolerability with no dose dependency of adverse events except for local injection reactions

Ienalumab Sjögren’s study showed dose dependent efficacy and good tolerability\textsuperscript{1-2}

**ESSDAI Responders w24**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo</th>
<th>5mg</th>
<th>50mg</th>
<th>300mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders</td>
<td>61.2%</td>
<td>61.7%</td>
<td>72.3%</td>
<td>89.4%</td>
</tr>
</tbody>
</table>

\textbf{28\% more responders} vs placebo with 300mg ianalumab

**Disease activity w24**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo</th>
<th>5mg</th>
<th>50mg</th>
<th>300mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease</td>
<td>0%</td>
<td>20%</td>
<td>40%</td>
<td>60%</td>
</tr>
<tr>
<td>Activity</td>
<td>20%</td>
<td>40%</td>
<td>60%</td>
<td>80%</td>
</tr>
</tbody>
</table>

\textbf{26\% more patients improved to low disease activity} and \textbf{only 2\% remained} at high disease activity with 300mg ianalumab

Systemic Lupus Erythematosus: A debilitating disease leading to permanent organ damage

Prevalence and treatment
- Prevalence: 0.02-0.07%
- 9:1 f/m predominance
- Adolescents and younger adults
- Mortality: 2-3 times higher than in general population
- Limited disease modifying treatment option

Rationale for ianalumab
- Autoantibody-immune complexes produce organ tissue damage
- BAFF levels correspond to disease severity lupus autoantibody production
- Depleting B-cells and blocking BAFF-R targets underlying disease mechanism
Ph2a trial in Systemic Lupus Erythematosus (SLE)

Randomized, double-blind, placebo-controlled, multicenter studies to evaluate the efficacy and safety of lanalumab

Study attributes

Composite primary endpoint:
- SRI-4 reduction under sustained corticosteroid tapering at week 24

Secondary endpoint:
- Safety
- Lupus low disease activity status
- Flare incidence

Estimated primary completion 2022

ClinicalTrials.gov identifier: NCT 03656562
Advancing ianalumab in a range of indications through 2020-25

<table>
<thead>
<tr>
<th>Indication</th>
<th>2020</th>
<th>2021</th>
<th>2022</th>
<th>2023</th>
<th>2024</th>
<th>2025</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sjögren’s Syndrome</td>
<td>Ph2b</td>
<td></td>
<td>Ph3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic Lupus Erythematosus</td>
<td>Ph2a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autoimmune Hepatitis</td>
<td>Ph2a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-cell Malignancies (Oncology)</td>
<td>Ph1/2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lupus nephritis (LN)</td>
<td></td>
<td></td>
<td>Ph3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Market potential (in G7 countries)

<table>
<thead>
<tr>
<th>Indication</th>
<th>Prevalence (targeted population)</th>
<th>Asset potential*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sjögren’s Syndrome</td>
<td>400,000+ (moderate to severe disease)</td>
<td>○○○ USD 1bn</td>
</tr>
<tr>
<td>Systemic Lupus Erythematosus</td>
<td>200,000+ (moderate to severe disease)</td>
<td>○ USD 1-2bn</td>
</tr>
<tr>
<td>AIH</td>
<td>120,000+ (non-responders to SoC)</td>
<td>○○○○ USD 2bn</td>
</tr>
<tr>
<td>B-cell malignancies</td>
<td>170,000+ (incidence)</td>
<td>○○○○ &gt;USD 2bn</td>
</tr>
<tr>
<td>Lupus nephritis</td>
<td>130,000+ (diagnosed patients)</td>
<td>○○○○ &gt;USD 2bn</td>
</tr>
</tbody>
</table>

LNA043

Modified recombinant human ANGPTL3 protein fragment that induces cartilage regeneration

Phase 2

Key highlights

- **300m people worldwide** suffering from osteoarthritis (OA), with knee OA most common form
- **No disease-modifying treatment** available
- Potential to become a first-in-class disease modifying treatment for osteoarthritis of the knee
- Early clinical trials showed cartilage anabolic effects and repair of damaged cartilage in patients with articular cartilage lesions in the knee
- Currently in Ph2b. FDA granted fast track designation. Filing expected ≥2026
- **US/EU**: Patent on composition of matter (2034/2034)\(^1\)

---

\(^1\) Patent term extensions and regulatory-based exclusivities are possible

OA = osteoarthritis
Osteoarthritis a progressive, debilitating condition without disease modifying therapies

Unmet need in Osteoarthritis (OA)

- 300 million people worldwide have OA\(^1\), most predominant is knee OA
- Single most common cause of disability in older adults\(^2\)
- No treatments can slow or reverse the damage in the joints
- Existing pharmacologic treatments only address symptoms
- OA joints continue to degenerate – often leading to joint failure and joint replacement
- As many as 20% of patients undergoing surgical joint replacement may be unsatisfied with their outcome\(^3\)
- High unmet need for disease modifying treatments

Goal

Develop disease-modifying treatment to:

- Reduce pain
- Improve function
- Prevent joint failure
- Prevent surgical joint replacement

LNA043, a modified recombinant human ANGPTL3 protein fragment, induces cartilage regrowth


LNA043 displayed a favorable safety profile in studies to-date.

LNA043 Ph2b ONWARDS trial in patients with knee OA

**Study endpoints**

- **Primary**: Change from baseline at 2 years in the cartilage thickness of the medial compartment of the knee as assessed by imaging

- **Key secondary**: Change from baseline in WOMAC pain and function at 2 years

**ONWARDS**: A 5-year, randomized, double-blind, placebo-controlled, multi-center study assessing the efficacy, safety, and tolerability of intra-articular regimens of LNA043 in patients with symptomatic knee osteoarthritis

**Table 1**: ClinicalTrials.gov Identifier: NCT04864392. WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.
LNA043 has the potential to become a disease modifying drug for knee OA with a blockbuster potential

### Market potential

<table>
<thead>
<tr>
<th>Indication</th>
<th>Prevalence</th>
<th>Asset potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee OA</td>
<td>165 m</td>
<td>![Asset potential](&lt;USD 1bn - USD 1-2bn - &gt;USD 2bn)</td>
</tr>
</tbody>
</table>

### Upcoming milestones for development program

<table>
<thead>
<tr>
<th>Knee OA</th>
<th>2021</th>
<th>2022</th>
<th>2023</th>
<th>2024</th>
<th>2025</th>
<th>2026</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph2b</td>
<td></td>
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</tbody>
</table>

*Primary readout*
Neuroscience
Our NS development strategy is focused on areas of high unmet need, with a strong late and early-stage pipeline

**Neuroscience strategy**

Ambition to deliver complete disease control for people living with **multiple sclerosis**

Slow disease progression for people with **neurodegenerative disease**

Deliver transformational symptomatic control and disease modification in **psychiatry**

Correct genetic deficits in children with **genetically driven** neurological conditions with Zolgensma®

**Assets highlighted today:** remibrutinib, Zolgensma®, branaplam, UCB0599

<table>
<thead>
<tr>
<th>Compound (indication)</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Registration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kesimpta® (Ped MS)</td>
<td></td>
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<tr>
<td>Mayzent® (Ped MS)</td>
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<tr>
<td>Remibrutinib (RMS)</td>
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<tr>
<td>CLS12311 (Immune Tolerization in MS)</td>
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<tr>
<td>Branaplam (HD)</td>
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<tr>
<td>BLZ945 (ALS)</td>
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<tr>
<td>UCB0599 (PD)</td>
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<td>NIO752 (PSP)</td>
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<tr>
<td>MIJ821 (MD)</td>
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<tr>
<td>ENV396 (Schizophrenia)</td>
<td></td>
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<tr>
<td>Zolgensma® (SMA IT)</td>
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</tbody>
</table>

**Disease area**

- Multiple sclerosis
- Neurodegeneration
- Psychiatry
- Pediatric neurology

**Partnerships across multiple platforms:** Cellerys in MS, UCB in PD, Sangamo in pediatric neurology

---

1. Option to acquire after Ph2
2. In partnership with UCB
3. Cadent sponsor of schizophrenia Ph1 trial

Note: bars in gantt chart indicate current phase of development.
**Remibrutinib**  
(LOU064)

Oral, covalent BTK (Bruton’s tyrosine kinase) inhibitor targeting immune cell signaling

---

**Key highlights**

- Despite the availability of several DMTs for the treatment of MS, **patients continue to experience disease activity**
- **BTKi inhibit activation of B-cells** and other innate immune cells with oral convenience
- Remibrutinib is a highly selective, potent covalent BTK inhibitor with **best-in-class potential in MS** as it may offer **comprehensive and sustained BTK inhibition** that allows maximizing on efficacy without compromising safety
- Ph2b data in CSU showed rapid and biologic-like efficacy, a positive benefit/risk profile and **good tolerability across entire dose range tested**
- **Direct to Ph3 in RMS. REMODEL-1 and 2 to begin enrollment in 2021**
- **US/EU**: Patent on compound (2034/2034)\(^1\)

---

DMT: Disease Modifying Therapy   MS: Multiple Sclerosis   CSU: Chronic Spontaneous Urticaria   RMS: Relapsing Multiple Sclerosis   DMT: Disease Modifying Therapy

\(^{1}\) Patent term extensions and regulatory-based exclusivities are possible
**Remibrutinib: potent and rapid BTK inhibition expected to translate into clinical efficacy and favorable safety profile**

**Remibrutinib shows potent BTK inhibition in human blood in vitro at clinically relevant concentrations**

![Graph showing BTK occupancy over time for Remibrutinib at different concentrations](image)

Data suggest that remibrutinib has **rapid reaction kinetics and rapidly reaches full BTK inhibition in relevant matrices such as human blood**

**Remibrutinib demonstrated good tolerability across the entire dose range tested with no safety signals**

**Key safety data include:**

- **✓ No dose dependent increase of, treatment interruption or discontinuation due to LFT elevations**
- **✓ No dose dependent cytopenias, treatment interruption or discontinuation due to low blood cell counts**
- **✓ No clinically relevant adverse events associated with BTK inhibitor class (e.g., infections, cytopenias, bleeding, hepatic events) across the dose range tested**

**Potential best-in-class profile based on positive benefit/risk profile. Ph3 studies in RMS initiating**

---

1. BTK - Bruton’s tyrosine kinase  
2. RMS – Relapsing Multiple Sclerosis  
3. LFT – Liver Function Test.
Initiating Ph3 trials with remibrutinib in relapsing multiple sclerosis

Remibrutinib

Potential best-in-class potency, selectivity and safety. May offer a more comprehensive and sustained BTK inhibition that allows for maximizing efficacy without compromising patient safety

- **Covalently binds** to the intracellular enzyme BTK in B cells and myeloid cells
- **Potent BTK inhibition** with brief and low systemic exposure which **minimizes risk** for AEs and drug-drug interactions
- CSU data – **no dose-limiting side effects** in Ph2a trial
- **Move directly into Ph3** in MS, with trials to start in Q4 2021

---

BTK - Bruton’s tyrosine kinase  
AE - Adverse Event  
CSU - Chronic Spontaneous Urticaria
REMODEL 1, 2 powered to show superiority vs teriflunomide

REMODEL 1 and 2 initiation expected in 2021

Objective
Compare the efficacy and safety of remibrutinib vs teriflunomide in Relapsing Multiple Sclerosis patients (adults)

1º endpoint
Annualized relapse rate (ARR)

Key 2º endpoints
- 3mCDP
- 6mCDP
- Gd-T1 lesions
- New/enlarging T2 lesions
- Neurofilament (NfL)
- NEDA-3

Randomized, double-blind, double-dummy, active comparator-controlled, fixed-dose, parallel-group, event-driven multi-center studies

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- 3mCDP
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- Gd-T1 lesions
- New/enlarging T2 lesions
- Neurofilament (NfL)
- NEDA-3

Population
18-55 years (inclusive), EDSS 0-5.5 (inclusive)
Diagnosis of MS according to 2017 McDonald diagnostic criteria; Relapsing MS (RRMS or SPMS)
At least: 1 relapse in the previous year, OR 2 relapses in the previous 2 years, OR 1 active Gd-enhancing lesion in 12 months prior to screening

Screening
≥ 18-55 years old RMS patients with EDSS 0-5.5

Baseline
remibrutinib
n=400 in each study (total n=800)
teriflunomide
n=400 in each study (total n=800)

Double-blind core treatment part

Open-label extension part

Long-term extension (5 years)

Readout expected Q2 2025

REMODEL 1, 2 powered to show superiority vs teriflunomide

REMODEL 1 and 2 initiation expected in 2021

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n=400 in each study (total n=800)
teriflunomide
n=400 in each study (total n=800)

Double-blind core treatment part

Open-label extension part

Long-term extension (5 years)

Readout expected Q2 2025
**Remibrutinib with significant commercial potential across indications**

<table>
<thead>
<tr>
<th>Market potential</th>
<th>2020</th>
<th>2021</th>
<th>2022</th>
<th>2023</th>
<th>2024</th>
<th>2025</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>CSU</td>
<td>~740k</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RMS</td>
<td>&gt; 0.5m</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prevalence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Asset potential</strong></td>
<td>&lt;USD 1bn</td>
<td>USD 1-2bn</td>
<td>&gt;USD 2bn</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Upcoming milestones for development program**

- **CSU Ph2b**
  - REMIX-1 and REMIX-2
  - Enrollment started November 2021
  - Submission in 2021

- **CSU Ph3**
  - REMODEL-1 and REMODEL-2
  - Enrollment start December 2021
  - Submission in 2025

RMS – Relapsing Multiple Sclerosis. CSU – Chronic Spontaneous Urticaria. 1. US-/EU5.
Zolgensma®
(onasemnogene abeparvovec)

AAV gene therapy for the treatment of spinal muscular atrophy

Marketed (IV); Phase 3 (IT)

Key highlights

- **Indications:**
  - Worldwide Incident SMA Population (2022): 6,800
  - Worldwide Prevalent SMA Population in 2026: 60,000
- Zolgensma is an essential one-time treatment that replaces the function of the missing or non-working SMN1 gene
- Zolgensma demonstrated age-appropriate development when used presymptomatically; consistent, significant benefit in symptomatic children; and durability 5+ years post-treatment
- OAV101 IT (STRONG) demonstrated significant efficacy with a rapid and sustained improvement in motor function
- US/EU: Patent on composition of matter (2033)/Regulatory-based exclusivity (2030)1
- Key upcoming milestones:
  - SMART (IV): anticipate data readout in 2023
  - STEER (IT): anticipate beginning enrollment in coming weeks

1. Patent term extensions and regulatory-based exclusivities are possible.
OAV101 IT would replace chronic administration for a large potential SMA population with significant unmet needs

Our goal is to make gene therapy foundational to all patients with SMA who may benefit

Existing therapies have limitations

- Require chronic use over person’s lifetime
- Work on the back-up SMN2 gene
- Risks and compliance challenges with administration

Potential patient population by 2026

- Annual incident patients (IV annual)
- Total prevalent patients (IT)

*OAV101 IT expected to file in 2025

SMA – Spinal Muscular Atrophy
SMN – Survival Motor Neuron
IV – Intravenous
IT – Intrathecal
*Assumes priority review.

Existing therapies have limitations

- Require chronic use over person’s lifetime
- Work on the back-up SMN2 gene
- Risks and compliance challenges with administration
New clinical trials will build on STRONG data, which reinforced potential best-in-category profile for OAV101 IT for later-onset SMA

92% Achieved ≥3 points at any visit within 1 year

A 3-point increase in HFMSE is agreed by experts to represent the minimum change considered clinically meaningful¹⁻³

Transformational efficacy with a 6-point mean increase in HFMSE⁴, 2x the clinically meaningful threshold

Rapid and Sustained Hammersmith Scores with gains seen across all five domains of motor function

Safety profile consistent with IV program

Comprehensive data package resolved FDA non-clinical safety concerns with DRG, partial hold lifted Aug 2021

References


OAV101 IT clinical program aims to confirm potential best-in-category profile for prevalent SMA

<table>
<thead>
<tr>
<th>STEER – Ph3</th>
<th>STRENGTH – Ph3b</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>Treatment-naive patients with SMA Type 2 aged 2-18 who can sit but have never walked (n=&gt;100)</td>
</tr>
<tr>
<td><strong>Overview</strong></td>
<td>Global, Ph3, sham-controlled</td>
</tr>
<tr>
<td><strong>Primary Objective</strong></td>
<td>HFMSE change from baseline at 52 weeks</td>
</tr>
<tr>
<td><strong>Status</strong></td>
<td>Patient enrollment anticipated in coming weeks</td>
</tr>
</tbody>
</table>

SMA – Spinal Muscular Atrophy
IT – Intrathecal
HFMSE – Hammersmith Functional Motor Scale-Expanded

References
Zolgensma® expanding clinical data set across IV and IT formulations

**Market potential**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Asset potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td></td>
</tr>
<tr>
<td>IT</td>
<td></td>
</tr>
</tbody>
</table>

- ○○○ <USD 1bn
- ○○ USD 1-2bn
- ○○○ >USD 2bn

**Addressable patients¹**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident (2022)</td>
<td>6,800</td>
</tr>
<tr>
<td>Prevalent (2026)</td>
<td>60,000</td>
</tr>
</tbody>
</table>

**Upcoming milestones for development program²**

<table>
<thead>
<tr>
<th></th>
<th>2020</th>
<th>2021</th>
<th>2022</th>
<th>2023</th>
<th>2024</th>
<th>2025</th>
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<tr>
<td>IV</td>
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<td></td>
<td></td>
<td></td>
<td>STRENGTH</td>
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</tr>
</tbody>
</table>

SMART: currently enrolling SMA patients who are ≤21kg in global Ph3b trial; anticipate data readout in 2023.

STEER: anticipate beginning to enroll treatment-naive patients with SMA Type 2 (aged 2 -18) in coming weeks for global Ph3 trial

STRENGTH: enrollment of patients aged 2-12 with SMA to receive OAV101 IT after discontinuing treatment with nusinersen and/or risdiplam anticipated to begin in 2H22.

¹ Worldwide incident and prevalent populations. ² End of arrow denotes estimated study completion.

IV – Intravenous  IT – Intrathecal  SMA – Spinal Muscular Atrophy
Key highlights

- ~70k people with Huntington’s Disease in G6 with high unmet need
- No approved disease modifying therapies that delay disease onset or slow progression
- Branaplam is an oral RNA splicing modulator that lowers HTT by driving HTT mRNA degradation and has the potential to be the first disease modifying therapy for HD
- Proof of concept demonstrated in pre-clinical and Ph1 studies and clinical data in children with SMA
- Ph2b VIBRANT-HD study aims to identify dose which reduces mHTT sufficiently to provide clinical benefit while maintaining adequate levels of HTT for normal function. To be initiated Q4 2021
- US/EU: Patent on compound (2033/2033)\(^1\)

Branaplam (LMI070)

Orally administered, small molecule RNA splicing modulator

Phase 2
## Branaplam lowers human HTT levels by driving HTT mRNA degradation

### Huntingtin mRNA

<table>
<thead>
<tr>
<th>Exon 49</th>
<th>Exon 50</th>
</tr>
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<tbody>
<tr>
<td><img src="image1.png" alt="RNA" /></td>
<td><img src="image2.png" alt="RNA" /></td>
</tr>
</tbody>
</table>

Intron is spliced out

### Huntingtin mRNA with Branaplam

<table>
<thead>
<tr>
<th>Exon 49</th>
<th>Exon 50</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image3.png" alt="RNA" /></td>
<td><img src="image4.png" alt="RNA" /></td>
</tr>
</tbody>
</table>

Promotes inclusion of a pseudoexon during transcription, which introduces premature stop codons.

... triggering mRNA degradation before translation, resulting in decreased production of both mutant and normal HTT protein.

---

**RNA** – Ribonucleic Acid  
**mRNA** – messenger Ribonucleic Acid  
**HTT** – Huntingtin  
**mHTT** – Mutant Huntingtin
Huntington's disease is a devastating neurodegenerative disease
Our goal is to transform care with the first oral disease-modifying therapy

**Huntington’s disease**

- Inherited disease affecting multiple generations of families, those with a mutated gene develop the disease
- Patients typically diagnosed age 30-50, disability leads to death within 15-20 years
- Characterized by progressive worsening in motor, cognitive and psychiatric symptoms
- Rare disease, ~70,000 diagnosed patients in US and EU
- No approved disease modifying therapies to delay disease onset or slow progression
- Earlier diagnosis by genetic testing expected as disease-modifying therapies become available

**Branaplam**

- Oral branaplam lowers Huntington protein, an opportunity for disease modification
- Non-invasive oral splice modulator for at-home administration
- Convenience of once weekly dosing
- May provide uniform HTT lowering throughout brain based on mouse models
- Broad exposure in peripheral tissues

**HTT** – Huntingtin
**Proof of concept demonstrated in Huntington’s Disease**

Ph1 results consistent with earlier preclinical data and clinical findings in SMA

---

**Ph1 healthy volunteer results support proof of concept and Ph2 initiation**

- Dose-dependent target engagement shown by inclusion of pseudoexon 50a in blood
- HTT mRNA and protein levels reduced in blood after single doses in healthy volunteers
- PK/PD supports weekly oral dosing
- Well-tolerated

---

**Market potential**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Asset potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huntington’s Disease</td>
<td>🟢🟢🟢 &lt;USD 1bn</td>
</tr>
</tbody>
</table>

---

**Branaplam lowering of HTT mRNA in SMA patients demonstrates target engagement and mechanism**

- HTT mRNA (assay location: exons 84-85, median % change from baseline)
- HTT mRNA (assay location: exons 36-37, median % change from baseline)
- HTT mRNA with pseudoexon inclusion (normalized relative quantity)

---

**Study Days**

- Median Percentage Change from Baseline

<table>
<thead>
<tr>
<th>Study Days</th>
<th>Average of Normalized Relative Quantities (Normalized to GUSB mRNA level)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-3</td>
<td>0</td>
</tr>
<tr>
<td>85</td>
<td>120</td>
</tr>
<tr>
<td>176</td>
<td>80</td>
</tr>
<tr>
<td>267</td>
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<td>358</td>
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<td>540</td>
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<td>631</td>
<td>-40</td>
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<tr>
<td>722</td>
<td>-60</td>
</tr>
<tr>
<td>813</td>
<td>-80</td>
</tr>
<tr>
<td>904</td>
<td>-100</td>
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<tr>
<td>995</td>
<td>-120</td>
</tr>
</tbody>
</table>

---

**HTT mRNA (assay location: exons 64-65, median % change from baseline)**

- Well-tolerated

---

**SMA – Spinal Muscular Atrophy**

- **HTT – Huntingtin**
- **mRNA – messenger Ribonucleic Acid**
- **PK – Pharmacokinetics**
- **PD – Pharmacodynamics**
**Ph2b VIBRANT-HD study to begin enrollment by year end**

**VIBRANT-HD**

<table>
<thead>
<tr>
<th>Cohort 1</th>
<th>Branaplam 56mg or PBO (n = 25)</th>
<th>Blinded Extension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Branaplam 112mg or PBO (n = 25)</td>
<td>Blinded Extension</td>
</tr>
<tr>
<td><strong>Cohort 2</strong></td>
<td>Branaplam 154mg or PBO (n = 25)</td>
<td>Blinded Extension</td>
</tr>
<tr>
<td></td>
<td>Branaplam 84mg or PBO (n = 25)</td>
<td>Blinded Extension</td>
</tr>
<tr>
<td></td>
<td>Branaplam 28mg or PBO (n = 25)</td>
<td>Blinded Extension</td>
</tr>
</tbody>
</table>

**OLE**

- Staggered 16w Dose Range Finding  R = 4:1

**Estimated primary completion 2025**

**Study attributes**

- Randomized, double-blind, placebo-controlled dose range finding study with open-label extension
- Primary end-points: % reduction in mHTT protein in CSF, number of treatment emergent adverse events and serious adverse events

**Ph2b VIBRANT-HD study**

- Randomized, double-blind, placebo-controlled dose range finding study with open-label extension
- Primary end-points: % reduction in mHTT protein in CSF, number of treatment emergent adverse events and serious adverse events

- Estimated primary completion 2025

- Study attributes
  - Evaluating safety, tolerability, pharmacokinetics and pharmacodynamics of branaplam when administered as weekly oral doses in participants with early manifest HD
  - Goal is to identify a dose of branaplam which is safe and well-tolerated, and lowers mHTT sufficiently in CSF to expect a clinical benefit in HD (35-50%)
UCB0599

Potential first-in-class, small molecule, alpha-synuclein misfolding inhibitor

Phase 2

Key highlights

- **10m people** with Parkinson’s Disease (PD) worldwide
- High unmet need given lack of disease-modifying therapies with Parkinson’s disease the fastest growing neurological disorder in prevalence, disability, and deaths
- Novartis and UCB have entered into a co-development and co-commercialization agreement for UCB0599 (alpha-synuclein misfolding inhibitor), with opt-in for UCB7853 (anti-alpha-synuclein antibody)
- With UCB0599, potential to transform care with first oral disease modifying therapy for PD
- Alpha-synuclein misfolding most prominent neuropathological hallmark of PD and primary step in disease progression
- In a preclinical model, UCB0599 reduced α-synuclein pathology and downstream neurodegeneration, as well as improved functional motor endpoints
- UCB0599 in Ph2 clinical development. UCB7853 in Ph1

---

Oncology
We are building on the strength of our Oncology pipeline to maximize impact for patients

**Oncology strategy**

**Leading Oncology pipeline**
with >30 NMEs in clinical development, reaching >1.2m patients

**Strengthen our core**
by maximizing existing and accelerating new assets
- Prioritize development in Breast, Prostate, Lung, AML/MDS and NHL
- Additional investment in asset-driven opportunities with breakthrough potential (e.g. NIS793)
- Expanding indications in areas with highest unmet need and moving into earlier lines of therapy – ultimately with curative intent

**Invest in innovative combinations and advanced therapy platforms**
- Explore innovative combinations across platforms to deepen responses and overcome resistance
- Expand our leading position in RLT with Lu-PSMA 617 in Prostate and beyond
- Invest in next generation of our C&G pipeline (e.g. YTB323)

**Assets highlighted today:**
Kisqali, 177Lu-PSMA-617, sabatolimab, JDQ443, TNO155, YTB323 & PHE885, Scemblix, NIS793

**Key late-stage programs in 2022 across platforms**

<table>
<thead>
<tr>
<th>Compound (indication)</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Registration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sabatolimab (MDS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sabatolimab (Unfit AML)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIS793 (mPDAC)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Canakinumab (Adjuvant NSCLC)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>177Lu-PSMA 617 (mCRPC; post-taxane)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>177Lu-PSMA 617 (mCRPC; pre-taxane)</td>
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</tr>
<tr>
<td>177Lu-PSMA 617 (mHSPC)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>YTB323 (2L DLBCL – transplant eligible)*</td>
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</tr>
<tr>
<td>YTB323 (2L DLBCL – transplant ineligible)*</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>JDQ443 (2/3L NSCLC)*</td>
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<td></td>
</tr>
<tr>
<td>Scemblix® (1L CML-CP)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kisqali® (Adjuvant BC)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Planned Phase 3 programs initiating in 2022
CANOPY-1 Ph3 data support further evaluation of canakinumab in lung cancer

**CANOPY-1**
- Did not meet primary endpoints: OS and PFS in previously untreated locally advanced or metastatic NSCLC
- Potentially clinically meaningful improvements in both PFS and OS among pre-specified subgroups of patients with inflammatory biomarkers; additional analyses ongoing
- Results support continued study of canakinumab in earlier stages of lung cancer, further evaluation of Pro-Tumor Inflammation in all lung cancer settings
- CANOPY-A study more closely reflect the CANTOS study population vs. CANOPY-1

### Study Table

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient population</th>
<th>Hypothesis</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>CANOPY-1</td>
<td>Metastatic NSCLC</td>
<td>Reduce progression of treatment resistant tumors</td>
<td>Primary endpoints of OS + PFS not statistically significant. Potentially clinically meaningful OS + PFS improvements in pre-specified subgroups (hs-CRP, other biomarker-defined subgroups)</td>
</tr>
<tr>
<td>CANOPY-2</td>
<td>Metastatic NSCLC</td>
<td>Canakinumab with docetaxel</td>
<td>Primary endpoint OS not met. No benefit observed.</td>
</tr>
<tr>
<td>CANOPY-A</td>
<td>Stage II-III NSCLC</td>
<td>Canakinumab after complete resection and adjuvant chemotherapy</td>
<td>To be determined</td>
</tr>
<tr>
<td>CANTOS</td>
<td>Stable post MI with elevated hsCRP</td>
<td>Alter tumor development in high risk population</td>
<td>Dose-dependent reduction in fatal/non-fatal lung cancer incidence</td>
</tr>
</tbody>
</table>

**Developing other potential pro-tumor inflammation pathway inhibitors, which are at various stages of development, incl. gevokizumab**

---

Key highlights

- **Kisqali**® has the most robust and rigorous body of evidence to be positioned as the standard of care (SOC) in 1L postmenopausal HR+/HER2- aBC, the largest patient population (~25K patients in the US each year, and up to ~370K patients globally)

- **Kisqali**® achieved the longest median overall survival (OS) ever reported in aBC (>5 years); it is the only CDK 4/6i with statistically significant OS across three Ph3 trials

- **Kisqali**® is being investigated in early BC in the Ph3 NATALEE study

- If successful, **Kisqali**® will be the only CDK4/6i with evidence supporting use in the intermediate and high-risk populations (>200K patient in the US & EU)

- NATALEE trial readout is event driven and expected in 2022

- US/EU: Patent on compound (2031/2032)

---

1. Includes extended patent terms. For additional information, please refer to the Novartis 20F 2020
HR+/HER2- BC, the largest segment in BC, remains an area of high unmet need

Estimated percentages of total breast cancer population

- HR+/HER2-: 70%
- TNBC: 20%
- HER2+: 10%

Metastatic Breast Cancer
- Extending OS without impacting quality of life (QoL) is the #1 treatment goal
- Kisqali® is the only CDK 4/6 inhibitor that significantly improved OS while maintaining or improving QoL consistently across all patient subgroups in three pivotal trials

Early Breast Cancer (eBC)
- 83% of breast cancers are diagnosed as eBC
- The treatment goal in eBC is to prevent disease recurrence while maintaining QoL
- Kisqali® is being investigated in eBC in the Ph3 NATALEE study
- The study is uniquely designed to assess benefit in both intermediate and high-risk populations

"...Improving patient outcome without putting additional burden on the patient is the challenge.... you would not accept a treatment which reduces quality of life."

US Oncologist (Market Research Study 2020)

Data Source: Kantar Health – US/EU5 Patient Metrics 2020

More intermediate risk patients diagnosed vs. high risk

>3x
Kisqali® has demonstrated significant OS benefit regardless of ET partner, line of therapy or menopausal status

Overall survival across HR+/HER2- Ph3 trials

<table>
<thead>
<tr>
<th>Months</th>
<th>Kisqali + ET</th>
<th>ET Monotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ML-2</td>
<td>63.9</td>
<td>51.4</td>
</tr>
<tr>
<td>ML-7</td>
<td>58.7</td>
<td>47.7</td>
</tr>
<tr>
<td>ML-3</td>
<td>53.7</td>
<td>41.5</td>
</tr>
</tbody>
</table>

- Kisqali is the only CDK 4/6 inhibitor with statistically significant overall survival proven across all three Ph3 trials
  - MONALEESA-2: the longest overall survival ever reported in Kisqali + Al (letrozole) in 1L postmenopausal patients $P=0.004$ (HR=0.765 [95% CI: 0.628-0.932])
  - MONALEESA-7: the longest overall survival reported in Kisqali + Al (NSAI + goserelin) in 1L premenopausal patients $P=0.00973$ (HR=0.71 [95% CI: 0.54-0.95])
  - MONALEESA-3: the longest overall survival reported in Kisqali + fulvestrant in 1L and 2L postmenopausal patients $P=0.00455$ (HR=0.726 [95% CI: 0.588-0.897])

- Overall survival increase of ~1 year or more across the trials
## Overall QoL was maintained or improved across all MONALEESA trials

<table>
<thead>
<tr>
<th>First line</th>
<th>MONALEESA-21,2</th>
<th>MONALEESA-73</th>
<th>MONALEESA-34</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved health-related QoL</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Maintained health-related QoL</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

Kisqali®-based combinations maintained or improved QoL and delayed time to CT by at least 4 years (incl. 1 year improvement vs. ET alone) in MONALEESA trials

AEs with Kisqali® are generally asymptomatic and do not impact activities of daily life

As eBC is a disease-free setting, QoL considerations become even more relevant

Additional data collection underway to assess patient preferences and long-term QoL on Kisqali®

NATALEE adjuvant trial could address large unmet need in eBC

NATALEE study design

What makes NATALEE unique?
- Broad patient population that includes patients with high and intermediate risk of recurrence2 (60% Stage III and 40% Stage II; stratification factor)3
- Longer treatment duration of 3 vs. 2 years (monarchE)
- Lower dose compared to metastatic setting (400mg vs. 600mg) to potentially improve overall tolerability without compromising efficacy in a disease-free setting

Study status
- Enrollment is complete
- Discontinuation rate remains within expectations based on current aggregate data
- Final readout is event-driven and anticipated in 2022

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1. eBC Patient - Adjuvant Breast Cancer Opportunity Assessment June 2020.  2. based on AJCC prognostic staging.  3. The trial did not require Ki-67% or other CDx for patient identification or stratification, but Ki-67% is part of the statistical analysis plan

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**Key highlights**

- **177Lu-PSMA-617** anticipated to address a **broad set of prostate cancer disease stages**
  - Post-taxane mCRPC (VISION trial, in registration)
  - Pre-taxane mCRPC and mHSPC patients in ongoing Ph3 studies PSMAfore and PSMAddition

- **177Lu-PSMA-617** is expected to be the **first-to-market radioligand therapy targeting >80% of prostate cancer patients who express PSMA**

- In the VISION trial, **177Lu-PSMA-617 reduced the risk of death by 38%, radiographic progression or death by 60%** in patients with mCRPC compared to SoC alone\(^2\), and ad-hoc analyses showed it delayed worsening of health-related quality of life and pain\(^3\)

- **US and EU approvals expected in 2022** (FDA granted Priority Review and BTD)

- US: Patents on composition of matter (2028-2034); patents in EU pending

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**177Lu-PSMA-617**

Radioactive lutetium-labelled small molecule targeting the prostate specific membrane antigen (PSMA)\(^1\)

---

**Registration**

<table>
<thead>
<tr>
<th>177Lu-PSMA-617</th>
<th>177Lu-PSMA-617 anticipated to address a broad set of prostate cancer disease stages</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Post-taxane mCRPC (VISION trial, in registration)</td>
</tr>
<tr>
<td></td>
<td>Pre-taxane mCRPC and mHSPC patients in ongoing Ph3 studies PSMAfore and PSMAddition</td>
</tr>
</tbody>
</table>

---

**References**

**177Lu-PSMA-617 RLT enables targeted delivery of radiation to tumor while limiting damage to surrounding normal tissue**

### Why 177Lu-PSMA RLT?

**Binds to PSMA**, highly expressed on >80% prostate cancer cells

Once bound and internalized, the Lutetium-177 radioisotope releases an energetic beta particle

This causes DNA breaks, disrupting target cell’s ability to replicate and/or triggering cell death

Designed to deliver radiation to target cells; may also impact neighboring cells

---

High remaining unmet medical need for patients with Prostate Cancer requires treatments with novel mechanisms of action

Prostate cancer is the 2nd most diagnosed cancer in men¹

Key facts

~35% develop metastases within 2 years of diagnosis²

Delay progression to metastatic disease

Novel MoAs are needed to

Stage of disease

Non-metastatic

BCR-PC | nmCRPC

Metastatic

mHSPC | mCRPC

~30% 5-year survival prognosis³

~10 months median OS⁴

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4. in men with progressive mCRPC after docetaxel and abiraterone and/or enzalutamide. Smith et al., Phase III Study of Cabozantinib in Previously Treated Metastatic Castration-Resistant Prostate Cancer: COMET-1, J Clin Oncol 34:3005-3013 ;
**177Lu-PSMA-617 reduced risk of death by 38%, and radiographic progression or death by 60% in patients with mCRPC (VISION)⁷,8**

**OS HR**: 0.62 (95%CI: 0.52, 0.74)

**Median OS**: 15.3 months (14.2, 16.9)⁴ vs. 11.3 (9.8, 13.5)⁴

**rPFS HR**: 0.40 (99.2%CI: 0.29, 0.57)

**Median rPFS**: 8.7 months (7.9, 10.8)⁵ vs. 3.4 (2.4, 4.0)⁵

Data support investigating ¹⁷⁷Lu-PSMA-617 in earlier lines of therapy

Two Ph3 studies in pre-taxane 1L / 2L mCRPC PSMAfore and mHSPC PSMAddition already underway

Studies in earlier disease stages under consideration

---

3. p<0.001, stratified log-rank test 1-sided.
4. 95% CI.
5. 99.2% CI, in line with hypothesis testing strategy.
Why explore $^{177}$Lu-PSMA-617 RLT in earlier lines of prostate cancer?

**Target expression**

PSMA is expressed 100 to 1000-fold higher in prostate cancer cells than in normal tissue, even at earlier stages of prostate cancer\(^1\)

**Synergy with existing standard of care**

$^{177}$Lu-PSMA-617 RLT to be used with Androgen Deprivation Therapy (ADT) and Androgen-Receptor Pathway Inhibitors (ARPI) which are reported to increase PSMA expression by 45 to 55% in mCRPC patients\(^2\)

**Safety**

The acceptable safety profile demonstrated in the VISION study supports providing $^{177}$Lu-PSMA-617 RLT to patients with better performance status in combination with active (ADT/ARPI) therapy

---

significant unmet need in earlier lines and stages of prostate cancer; two Phase 3 studies ongoing

Prostate cancer incidence¹
US, EU5, JP (‘000)

>80% of patients express PSMA

<table>
<thead>
<tr>
<th>Setting</th>
<th>Study</th>
<th>Status</th>
<th>Expected filing</th>
<th>Asset potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>mCPRC 3/4L (post-taxane)</td>
<td>VISION</td>
<td>Completed</td>
<td>FDA complete EMA complete</td>
<td></td>
</tr>
<tr>
<td>mCPRC 1L/2L (pre-taxane)</td>
<td>PSMAfore</td>
<td>Recruiting</td>
<td>2023</td>
<td></td>
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<tr>
<td>mHSPC</td>
<td>PSMAAddition</td>
<td>Recruiting</td>
<td>2024</td>
<td></td>
</tr>
<tr>
<td>nmCRPC</td>
<td>Under evaluation</td>
<td></td>
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</tr>
</tbody>
</table>

BCR² nmCRPC³ mHSPC⁵ mCPRC⁶ 1L mCPRC⁶ 2L mCPRC³ 3L+ Under Evaluation VISION PSMAfore PSMAAddition

1. 2020 Incidence based on Kantar Health Cancer/Multip Treatment Architecture US, EU5, JP (February 2021). Incidence incl. patients in long-term response from prior line, who die before receiving therapy, progress but do not receive therapy, and receive systemic therapy. 
2. Localised high risk prostate cancer including adjuvant and neoadjuvant eligible. 
5. Metastatic hormone-sensitive prostate cancer. 
7. NVS estimation based on current treatment rates with 15% of 2L patients assumed to have progressed on both a first ARDT and taxane treatment.

Aim to expand in earlier lines of prostate cancer treatment

Market size:
- ○○○ <USD 1bn
- ○○ USD 1bn – 2bn
- ○○○ >USD 2bn

141
Growing Prostate Cancer RLT pipeline
Potential to address different prostate cancer disease stages via PSMA-targeted therapy

<table>
<thead>
<tr>
<th>Product</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Filing</th>
<th>Status</th>
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<tr>
<td>$^{177}$Lu PSMA-617</td>
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<td>FDA and EMA submission complete</td>
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<td>$^{68}$Ga PSMA-11</td>
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<td>FDA and EMA submissions complete</td>
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<td>$^{225}$Ac PSMA-617</td>
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<td>Ph1 study recruiting</td>
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<td>$^{68}$Ga PSMA-R2</td>
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<tr>
<td>$^{18}$F CTT1057</td>
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<td></td>
<td>Ph2/3 &amp; 3 studies recruiting</td>
</tr>
</tbody>
</table>

Therapeutic
Imaging / diagnostic
**Sabatolimab**  
(MBG453)

**Anti-TIM-3 monoclonal antibody**

**Phase 3**

**Key highlights**

- Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML) are related myeloid disorders with very high unmet medical need.
- Sabatolimab is a potential **first-in-class immuno-myeloid therapy** that binds to TIM-3, a target expressed on immune and leukemic cells\(^1\)\(^-\)\(^5\).
- Early clinical data show that sabatolimab + HMA is **safe and well tolerated**, and demonstrated **durable clinical benefits** in patients with vHR/HR-MDS and ND-AML, including patients with adverse risk mutations.
- Pivotal study in **HR-MDS** ongoing, readout and **submission expected 2022-2023**; Ph3 recruitment is ahead of target, and close to completion.
- Ph2 study in Unfit AML ongoing since 2020; readout projected for 2023 will inform subsequent Ph3.
- US/EU: Patent on composition of matter (2035/2035)\(^6\).

---

6. Patent term extensions and regulatory-based exclusivities are possible.
Myelodysplastic syndrome and acute myeloid leukemia are related myeloid disorders with high unmet medical need

**Limited durability**

Poor prognosis and lack of durable benefits (e.g. responses, survival, QoL)

**Median Overall Survival (mOS):**
- ~12 months for HR-MDS¹
- ~15 months for Unfit AML²

**Tolerability**

Significant toxicity impacts the benefit of current therapies (intensive chemotherapy, hypomethylating agents, HSCT)

**Lack of innovation**

No treatment innovation in over 15 years³ in HR-MDS

---

<table>
<thead>
<tr>
<th>MDS</th>
<th>AML</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Age of Diagnosis</strong></td>
<td>~76 years¹</td>
</tr>
<tr>
<td><strong>Annual Incidence in US⁵</strong></td>
<td>~19K/year</td>
</tr>
<tr>
<td><strong>Patient Population with High Unmet Medical Need</strong></td>
<td>Higher Risk-MDS (HR-MDS) is a more aggressive type with worse prognosis and a higher chance of progressing to AML</td>
</tr>
</tbody>
</table>

---

MDS = Myelodysplastic Syndromes; AML = Acute Myeloid Leukemia.

IPPS (International Prognostic Scoring System) risk categorization in MDS. “Higher Risk” ~34% (11% High Risk, 23% Intermediate-2 risk).

2. VIALE-A phase 3 study, C D. DiNardo et al. NEJM 2020 AML.
Sabatolimab is a novel immuno-myeloid therapy that targets TIM-3 on immune and leukemic cells

**Sabatolimab MoA**

**Timelines for the Approval and Introduction into Clinical Practice**

Relative expression of TIM-3 on immune and leukemic cells

**References**


**Sabatolimab**

**Kisqali®**

**177 Lu-PSMA-617**

**> Saba tollimab**

**JDQ443**

**T-Charge™**

**Sceblix**

**NIS793**

**NIBR and Technology Platforms**

**Appendix**

**Respiratory & Allergy**

**Submission schedules**

**References**

**AML, acute myeloid leukemia; FcγR, Fc gamma receptor; HSC, hematopoietic stem cell; LSC, leukemic stem cell; MDS, myelodysplastic syndrome; NK, natural killer; TIM-3, T-cell immunoglobulin domain and mucin domain-3.**

**Expressed on myeloid immune cells and leukemic stem cells (LSC) but not on normal hematopoietic stem cells1-5, making it a promising target in MDS/AML2,4,6**

Sabatolimab is a potential first-in-class IgG4 anti-TIM-3 monoclonal antibody (mAb), which is hypothesized to:

- **Bind TIM-3 on immune cells**, enhancing antileukemic immune activation and phagocytic killing of LSCs and blasts9-12
- **Directly target TIM-3 on LSCs**, inhibiting TIM-3/galectin-9-driven self-renewal9,10
EHA and ASH newsflow 2021: Durable clinical benefit with sabatolimab, unique MoA as an immuno-myeloid therapy

Final analysis of sabatolimab + HMA Ph1 study

- Durable responses, including in patients with adverse risk mutations (TP53, RUNX1, ASXL1)
- Clinically significant immune-mediated AEs were rare

Biomarker analysis of Ph1 patient samples

- Single cell RNAseq analysis: Unlike PD-1 and CTLA-4, TIM-3 is expressed on leukemic, dendritic, myeloid, and NK cells. The effects of TIM-3 blockade were mainly observed in these cells
- Implication of IL-1β: Sabatolimab + HMA downregulates pro-inflammatory cytokine IL-1β in leukemic blast cells, but conversely upregulates IL-1β in myeloid immune cells

1. Brunner A et al, ASH2021 oral presentation, Abstract #244.  
3. Wei A. et al, EHA2021 oral presentation, Abstract #S168
STIMULUS program fully deployed to establish sabatolimab as a backbone across myeloid diseases

### HR-MDS

**STIMULUS-MDS1**
Ph2, HMA combination, enrollment complete

**STIMULUS-MDS2**
Ph3, HMA combination, enrollment ahead of schedule, and expected to complete by 2021

**STIMULUS-MDS3**
Ph2, HMA + venetoclax combination

**STIMULUS-MDS-US**
Ph2, combination with any approved HMA including the oral decitabine (INQOVI)

### AML

**STIMULUS-AML1**
Ph2, HMA + venetoclax combination, Unfit AML

**STIMULUS-AML2**
Ph1b/2, monotherapy and HMA combination, AML post-ahsct, in remission but MRD+

### Novel combinations

**MDS/AML**
Ph1b, HDM201 combination

**LR-MDS**
Ph1b, mono and combination with NIS793, canakinumab

**Myelofibrosis**
Ph1b/2, ruxolitinib combination

#### Indication

<table>
<thead>
<tr>
<th>Indication</th>
<th>G7 incidence</th>
<th>Asset potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR-MDS</td>
<td>~22,000</td>
<td></td>
</tr>
<tr>
<td>Unfit AML</td>
<td>~15,000</td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>&lt;USD 1bn</td>
<td></td>
</tr>
<tr>
<td>LR-MDS</td>
<td>USD 1bn – 2bn</td>
<td></td>
</tr>
<tr>
<td>MRD*</td>
<td>&gt;USD 2bn</td>
<td></td>
</tr>
</tbody>
</table>

#### STIMULUS-MDS1:
Ph2 randomized, double-blind, 2 primary endpoints: CR, PFS (event-driven)

#### STIMULUS-MDS2:
Ph3 randomized, double-blind, primary endpoint: OS (event-driven)

Ph3 recruitment ahead of target, and very close to completion; readout and first submission expected 2022-2023

---

**Key highlights**

- **KRAS\(^{G12C}\)** occurs in ~13% of NSCLC and is a clinically validated target.
- JDQ443 is a *selective, covalent and orally bioavailable* KRAS\(^{G12C}\) *inhibitor* that binds the mutant cysteine residue, and irreversibly traps KRAS\(^{G12C}\) in a GDP-bound, inactive state.
- In preclinical studies, JDQ443 potently *inhibits* KRAS\(^{G12C}\)-driven oncogenic signaling and *demonstrates* dose-dependent activity.
- Emerging data from our ongoing Ph1 study supports *initiation of a pivotal Ph3 randomized study in 2L KRAS\(^{G12C}\) mutant NSCLC in H1 2022*.
- FIH data will be presented at an upcoming cancer congress in H1 2022.
- **JDQ443 will serve as the anchor for multiple combination strategies** designed to significantly enhance efficacy of G12C therapy and improve outcomes of patients with KRAS\(^{G12C}\)-driven cancers.
- Patents pending.
Lung cancer remains the deadliest cancer among all cancer types; KRAS\(^{G12C}\) mutation represents ~13% of NSCLC

- Lung cancer is the leading cause of cancer death worldwide\(^1\)
- KRAS mutation occurs in 1 of 4 NSCLC patients; G12C accounts for ~50% of KRAS mutations
- The clinical activity of sotorasib (Lumakras) in KRAS\(^{G12C}\) mutant NSCLC is relatively modest (ORR 37%, median PFS 6.8 mos)\(^2\)
- Multiple KRAS\(^{G12C}\) inhibitors are in clinical development

Resistance to KRAS\textsuperscript{G12C} inhibitors emerges early and is polyclonal

One G12Ci-resistant patient with 10 distinct genetic alterations

<table>
<thead>
<tr>
<th>Acquired KRAS Alterations</th>
<th>Acquired RTK/RAS/MEK/PI3K Alterations</th>
<th>Acquired Gene Fusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Type</td>
<td>Histologic Features at Resistance</td>
<td>KRAS\textsuperscript{G12C} at Resistance</td>
</tr>
<tr>
<td>Tissue</td>
<td>Adenocarcinoma to squamous-cell carcinoma</td>
<td>Detected</td>
</tr>
<tr>
<td>cDNA</td>
<td>Adenocarcinoma</td>
<td>Not detected</td>
</tr>
<tr>
<td>Tissue and cDNA</td>
<td>Not assessed</td>
<td></td>
</tr>
</tbody>
</table>

Awad et al., NEJM 384(25): 2382-93, 2021

Heterogeneity of resistance mechanisms in G12C-driven cancers

**JDQ443: MoA and preclinical studies**

JDQ443 (NVP-JDQ443) is a selective, covalent and orally bioavailable investigational KRAS\textsuperscript{G12C} inhibitor that binds under the switch II loop, and irreversibly traps KRAS\textsuperscript{G12C} in a GDP-bound, inactive state.

In preclinical models, JDQ443 potently inhibited KRAS\textsuperscript{G12C} cellular signaling and proliferation in a mutant-selective manner, and demonstrated dose-dependent anti-tumor activity, with comparable efficacy as sotorasib in KRAS\textsuperscript{G12C} mutant tumor xenografts.
**KontRASSt|01: Ph1 JDQ443 study**

### Dose escalation: Phase 1b

**A** JDQ443 monotherapy
- KRAS G12C-mutated solid tumors

**B** JDQ443 + TNO155
- KRAS G12C-mutated solid tumors

### Dose expansion: Phase 2

- **2/3L KRAS G12C-mutated NSCLC**
- **≥3L KRAS G12C-mutated CRC**
- **2/3L KRAS G12C-mutated NSCLC (KRAS<sup>G12C</sup> naïve)**
- **3/4L KRAS G12C-mutated NSCLC (KRAS<sup>G12C</sup> pretreated)**
- **≥3L KRAS G12C-mutated CRC**

**C** JDQ443 + tislelizumab
- 2/3L KRAS G12C-mutated NSCLC

**D** JDQ443 + TNO155 + tislelizumab
- 2/3L KRAS G12C-mutated NSCLC

MTD, maximum tolerated dose RD, recommended dose

Currently enrolling

KRAS G12C-mutated solid tumors

- JDQ443 monotherapy
- JDQ443 + TNO155
- JDQ443 + TNO155 + tislelizumab

- MTD, maximum tolerated dose RD, recommended dose
The KontRAS̩t program will enable launching JDQ443 mono and combos for KRAS\(^{G12C}\) NSCLC patients

JDQ443 monotherapy for KRAS\(^{G12C}\) mutant NSCLC

**KontRAS̩t | 01** (Ph1/2)

**KontRAS̩t | 02** (Ph3)

JDQ443 combinations for KRAS\(^{G12C}\) mutant NSCLC (G12Ci naïve or pretreated)

**KontRAS̩t | 01** (Ph1/2)

**KontRAS̩t | 03** (Ph1/2)

Expansion to 1L KRASG12C mutant NSCLC

Studies to be defined based on emerging data
**Key highlights**

- SHP2 is a protein tyrosine phosphatase that drives cancer growth signaling in collaboration with receptor tyrosine kinases (RTKs) and KRAS; it is also a transducer of PD-1 signaling

- **TNO155 is a first-in-class inhibitor of SHP2** that acts as an intramolecular glue to effect allosteric inhibition

- Pre-clinical data support combination of TNO155 with a range of tyrosine kinase inhibitors as well KRAS\(^{G12C}\) inhibitors, and we have adopted a broad clinical combination strategy to blanket the MAPK pathway with 8 ongoing combination trials in solid tumors

- The Ph1 study of TNO155 has established safety, PK/PD and RDE, enabling the investigation of multiple combination strategies

- TNO155 has shown preliminary promising activity in combination with KRAS\(^{G12C}\) inhibitors in G12C-driven cancers

- US/EU: Patent on compound (2035/2035)\(^{1}\)

---

1. Patent term extensions and regulatory-based exclusivities are possible
TNO155: A first-in-class inhibitor of SHP2 and ideal combination partner for targeted and checkpoint therapies

First SHP2i to enter the clinic

**PDB, 5EHP**

Inactive form stabilized

Ideal drug-like properties (e.g. high permeability, solubility, no CYP450 inhibition, ideal preclinical PK profile)

Required for RTK signaling

RTK-SHP2-RAS-MAPK pathway activation has been implicated across the majority of human cancers

Downstream transducer of PD-1

SHP2 is a downstream transducer of PD-1 signaling, a critical immune checkpoint in human malignancies

LaMarche, M., AACR 2020.
Strong pre-clinical synergy between SHP2i and KRAS$^{G12C}$i supports TNO155 + G12Ci combination approach

**Mechanism of synergy**

KRAS$^{G12C}$ still cycles between GTP- and GDP-bound states and SHP2i enriches the GDP-bound KRAS$^{G12C}$, which G12Ci binds (enhances target engagement)

SHP2i suppresses feedback activation of wildtype KRAS, NRAS, HRAS post ERK inhibition by G12Ci (prevents pathway re-activation)

Other oncogene-driven cancers may be susceptible to SHP2i based combinations

Major classes of resistance mechanisms to targeted therapies

Off-target mechanisms drive the majority of resistance to next generation targeted therapies

Off Target

Mutations in the drug target
Bypass signalling
Mutations in downstream effectors


EGFR

Post 1\textsuperscript{st}/2\textsuperscript{nd} gen TKI
Post 3\textsuperscript{rd} gen TKI (1L)

Off target

ALK

Post 2\textsuperscript{nd} gen TKI
Post 3\textsuperscript{rd} gen TKI (3L+)

Off target

Other oncogene-driven cancers may be susceptible to SHP2i based combinations
Ph1 first-in-human study of TNO155: Optimizing dose and schedule to enable combinations

**Comprehensive dose escalation establishes safety, PK/PD and RDE of TNO155**

Data cut-off: August 17, 2021
Primary objective: DLTs, safety, tolerability
Secondary objective: ORR, DCR, PFS, DOR, PK, pharmacodynamics
Treatment until unacceptable toxicity, disease progression, or patient/physician decision

**Manageable safety profile with mostly low grade AEs enable TNO155 combinations**

*NCT03114319*. Source: Brana et al., ASCO 2021.

Ph1 first-in-human study of TNO155: Optimizing dose and schedule to enable combinations

**Comprehensive dose escalation establishes safety, PK/PD and RDE of TNO155**

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**Manageable safety profile with mostly low grade AEs enable TNO155 combinations**

*NCT03114319*. Source: Brana et al., ASCO 2021.
# Multiple TNO155 combinations are being explored clinically

<table>
<thead>
<tr>
<th>Combination</th>
<th>Disease</th>
<th>Est. frequency</th>
<th>FPFV</th>
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<tbody>
<tr>
<td>TNO155 + EGF816</td>
<td>EGFR mutant NSCLC, post osimertinib</td>
<td>10-40% of NSCLC</td>
<td>September 2020</td>
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<tr>
<td>TNO155 + lorlatinib</td>
<td>ALK+ NSCLC, post next generation ALK TKI</td>
<td>3-5% of NSCLC</td>
<td>March 2021</td>
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<tr>
<td>TNO155 + dab/tram</td>
<td>BRAF V600-mut CRC</td>
<td>~10% of CRC</td>
<td>July 2021</td>
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<tr>
<td>TNO155 + dab/LT462</td>
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<tr>
<td>TNO155 + PDR001</td>
<td>KRAS(^{G12C}) NSCLC, ≥1% PD-L, post-chemo and aPD-(L)1</td>
<td>~13% of NSCLC</td>
<td>August 2019</td>
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<tr>
<td>TNO155 + ribociclib</td>
<td>KRAS-mut CRC, post-SoC, per local standard</td>
<td>30-40% of CRC</td>
<td>August 2019</td>
</tr>
<tr>
<td>TNO155 + JDQ443</td>
<td>KRAS(^{G12C}) NSCLC and CRC</td>
<td>~13% of NSCLC, ~4% of CRC</td>
<td>June 2021</td>
</tr>
<tr>
<td>TNO155 + MRTX849</td>
<td>KRAS(^{G12C}) NSCLC and CRC</td>
<td>~13% of NSCLC, ~4% of CRC</td>
<td>April 2020</td>
</tr>
<tr>
<td>TNO155 + sotorasib</td>
<td>KRAS(^{G12C}) NSCLC and CRC</td>
<td>~13% of NSCLC, ~4% of CRC</td>
<td>November 2021</td>
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</tbody>
</table>
Expanding the Novartis MAPK pipeline to enable innovative combination strategies

- KRAS-MAPK is one of the most highly validated oncogenic pathways in human cancer
- Novartis is exploring multiple combination strategies, including:
  - JDQ443-based combinations in KRAS\textsubscript{G12C}-driven NSCLC, CRC and other solid tumors
  - TNO155-based combinations in multiple different indications, including KRAS\textsubscript{G12C}-driven cancers
  - LXH254-based combinations in NRAS or BRAF mutant melanoma, KRAS mutant NSCLC, atypical BRAF mutant NSCLC
  - Dabrafenib/LTT462 and dabrafenib/trametinib triplet combinations in BRAF V600 mutant CRC
- IAG933, a YAP/TEAD inhibitor, has entered the clinic with FPFV October 2021 (NCT04857372)
T-Charge™

**Key highlights**

- The T-Charge™ platform aims to revolutionize CAR-T cell therapy with a rapid, expansion-less manufacturing process, expected to increase CAR-T potency and reduce turnaround time and COGS.
- Preclinical studies demonstrate that YTB323 and PHE885, our lead candidates on the T-Charge™ platform, retain the naive and stem cell memory T-cell subpopulations from the original patient apheresis; these are associated with improved antitumor efficacy.
- YTB323 is a novel autologous anti-CD19 CAR-T cell therapy for B-cell malignancies, including DLBCL, which is the most common type of NHL, accounting for ~31% of all NHL in Western countries.
- PHE885 is a novel autologous fully human BCMA-directed CAR-T cell therapy investigated in Multiple Myeloma (MM), which comprises ~10% of hematologic malignancies.
- Emerging safety and preliminary efficacy data support ongoing Ph1 studies; updated data will be presented at the upcoming ASH meeting.
- Novartis is developing T-Charge™ as the foundation for multiple new CAR-T therapies.
- YTB323: US/EU patent on composition of matter/use (2031/2031); PHE885: Patents pending.
**T-Charge™: NIBR developed, novel CAR-T technology platform serving new therapies in Novartis pipeline**

- **Minimal ex vivo culture to maximize in vivo expansion**
  - Apheresis
  - Transduction
  - T-Charge manufacturing process time will be less than 2 days
  - With T-Charge, CAR-T cells can expand within their natural environment when infused into the patient
  - 10-50 fold fewer CAR-T cells infused compared to existing CAR-T therapies

- **T-Charge preserves T-cell “stemness,” an important T-cell characteristic closely tied to its therapeutic potential**
  - Flow cytometry shows:
    - T-Charge retains naive / Tscm cells (CD45RO-/CCR7+)
    - In contrast, the traditionally generated product consists mainly of central memory T-cells (Tcm) (CD45RO+/CCR7+)
Two lead constructs in development on T-Charge™
Designed to provide fast access to therapy, increased rates of response and longer durability

YTBS323 is an autologous CD19-directed CAR-T cell therapy

- YTBS323 is in Ph1 for B-cell malignancies such as r/r DLBCL and adult ALL
- Utilizes the FMC63 domain for CD19 recognition and 4-1BB costimulatory domain
- While using the same CAR transgene as tisagenlecleucel, the innovative T-Charge manufacturing process of YTBS323 leads to a differentiated product with unique characteristics

PHE885 is an autologous BCMA-directed CAR-T cell therapy

- PHE885 is a fully human investigational CAR-T cell therapy in Ph1 for multiple myeloma
- Utilizes a novel, highly potent extracellular scFv targeting B-cell maturation antigen (BCMA), and includes the 4-1BB co-stimulatory to enhance T-cell survival
YTB323 for B-cell Malignancies: 75% CR at ASH

Revolutionary autologous CD19 CAR-T cell therapy with novel biological attributes

**Ph1: YTB323 in r/r DLBCL, N=14**

- FIH study in r/r DLBCL and adult ALL is ongoing
- Promising preliminary efficacy: All patients dosed at $12.5 \times 10^6$ are ongoing and have responded to treatment (PR, cCR or CR)^2
- Preliminary safety profile similar to that reported for tisagenlecleucel in JULIET study

1. cCR: continuous CR for patients in CR post bridging therapy.
2. 2 patients in DL2 with PD were given a lower than planned dose ($6.8$ and $7.4 \times 10^6$).

Reference: 1. Flinn et al. American Society of Hematology Annual Meeting; December 11-14, 2021; Atlanta, GA.

Presented at ASH 2021
PHE885 in Multiple Myeloma: 100% ORR at ASH
Revolutionary autologous BCMA CAR-T cell therapy with novel biological attributes

Ph1: PHE885 in r/r MM, N=7

- Preliminary data shows encouraging clinical activity in patients with r/r MM
  - 6/6 patients (100%) that were infused had a clinical response, that was achieved quickly and deepened over time
  - MRD was evaluable for 3 patients at 1 month after treatment, all were MRD negative (2 MRD negative 10^{-6} and 1 MRD negative 10^{-5})
  - The dose-finding phase of the FIH study is ongoing

- 6/6 patients (100%) experienced CRS, 2/6 (33%) had a grade 3 event (Lee et al 2014)
- Two patients experienced grade 2 neurotoxicity related to PHE885; both events were non-serious and temporally associated with grade 3 CRS

- 2/6 patients achieved sCR at 3 months

BCMA, B-cell maturation antigen; CR, complete response; MRD, mean residual disease; PR, partial response; sCR, stringent complete response; VGPR, very good partial response. Reference: 1. Sperling A et al. American Society of Hematology Annual Meeting; December 11-14, 2021; Atlanta, GA. Poster 3864.
Key highlights

- Despite advances in chronic myeloid leukemia (CML) care, many patients are at risk of disease progression and sequential tyrosine kinase inhibitor (TKI) therapy may be associated with increased resistance and intolerance.

- By Specifically Targeting the ABL Myristoyl Pocket (STAMP), asciminib specifically inhibits the growth of BCR-ABL1-dependent cancer cells and is designed to overcome resistance and minimize off-target activity.

- FDA accelerated approval, based on ASCEMBL trial, granted in Oct 2021
  - Approved in adult patients with Philadelphia chromosome positive (Ph+) CML in Chronic Phase (CP), previously treated with two or more TKIs (~10K patients)
  - Full approval for the treatment of adult patients with Ph+ CML in CP with T315I mutation (~1K patients)

- ASC4FIRST study investigating asciminib vs. investigator-selected TKI in 1L CML patients has started and is in the recruitment stage.

- US/EU: Patent on compound (2033/2033)¹

¹. Patent term extensions and regulatory-based exclusivities are possible
**SCEMBLIX®**: A novel treatment approach to address high unmet need in CML

**Patient Journey in CML, treatment options and preferences**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Addressable patients</th>
<th>Asset potential</th>
<th>Approximate 24K patients worldwide (G7) are receiving 2L treatment and many may need a switch to 3L due to resistance and/or intolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1L CML-CP</td>
<td>64K</td>
<td>&lt;USD 1bn</td>
<td>(G7) are receiving 2L treatment and many may need a switch to 3L due to resistance and/or intolerance</td>
</tr>
<tr>
<td>3L+ CML-CP</td>
<td>10.5K</td>
<td>&lt;USD 1bn – 2bn</td>
<td>(G7) are receiving 2L treatment and many may need a switch to 3L due to resistance and/or intolerance</td>
</tr>
<tr>
<td>T315I CML-CP</td>
<td>1.1K</td>
<td>&gt;USD 2bn</td>
<td>(G7) are receiving 2L treatment and many may need a switch to 3L due to resistance and/or intolerance</td>
</tr>
</tbody>
</table>

**SCEMBLIX® will address high unmet medical need**

- Currently, **10-15% of CML patients progress to 3L**, where failure rate can be as high as **75%**
- Additionally, a significant number **remain in 2L** due to lack of appropriate options
- **T315I mutation confers resistance to all** ATP-binding TKIs except ponatinib
- **Potential to provide another treatment option in 1L CML**, as ~50% of patients relapse on imatinib or are refractory/intolerant to imatinib, and >30% of patients suffer from TKI-related non-hematological AEs

---

Asciminib is the first BCR-ABL inhibitor that works by STAMP (Specifically Targeting the ABL Myristoyl Pocket)

**Constitutively active BCR-ABL1**

- BCR
- ABL1
- Displaced N-terminal
- ATP-binding site
- Myristoyl pocket
- Asciminib

**Inactive ABL1**

- BCR
- ABL1
- ATP-binding site
- Myristoyl pocket
- Asciminib

Asciminib is different from ATP-competitive TKIs – by Specifically Targeting the ABL Myristoyl Pocket (STAMP) it maintains activity against cells expressing clinically observed ATP-binding TKI resistant mutations. In earlier lines of treatment, asciminib may combat emergence of mutations at the BCR-ABL1 ATP-binding site. The specificity of asciminib for the ABL kinase family minimizes off-target activity.

Launching SCEMBLIX®, a STAMP inhibitor with potential to transform the standard of care in CML

In ASCEMBL study, asciminib showed a nearly two-fold improvement in MMR rate supporting its clinical benefit in heavily pre-treated patients

Clinically meaningful efficacy of asciminib in patients with CML-CP harboring the T315I mutation

Major Molecular Response (MMR) rate at Week 24

- Asciminib: 25.5% (N=157)
- Bosutinib: 13.2% (N=76)

Difference: 12.2% (95% confidence interval: 2.19, 22.30, two-sided p-value: 0.029) (per the Cochran-Mantel-Haenszel test which is stratified by baseline major cytogenetic response status)

Data on file, not published

Confidence interval by week 24: Ponatinib pre-treated (16.3 – 48.7); Ponatinib naïve (36.8 – 77.0), All patients (27.7 – 57.8)
ASC4FIRST: Pivotal trial testing asciminib in 1L CML-CP

The trial has multiple primary endpoints:
- Superiority of asciminib vs investigator choice TKI as assessed by MMR at 48 weeks and/or
- Superiority of asciminib vs IMA subgroup alone as assessed by MMR at 48 weeks

Achievement of MMR (BCR-ABL1 \(\leq 0.1\%\)) is associated with higher rates of EFS, PFS and OS\(^1\)

FPFV achieved in Q4 2021

---

CML-CP, chronic myeloid leukemia in chronic phase. ELTS, EUTOS long-term survival score. EUTOS, European Treatment and Outcome Study. QD, once daily. MMR, major molecular response (BCR-ABL1 \(\leq 0.1\%\)). TKI, tyrosine kinase inhibitor.

a. Patients will remain on study for 5 years after the last patient first dose. b. Patients who discontinue early will continue to be followed up for survival and disease progression until the end of the study. 1. Saussele S et al., Leukemia; 32(5): 1252-8, 2018; Hochhaus et al., Leukemia; 34:966-94, 2020

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R&D DAY | DECEMBER 2021 | NOVARTIS INVESTOR RELATIONS
Key highlights

- Annually, approx 500k pts worldwide are diagnosed with PDAC and 1.9M with CRC\(^1\)
- TGFβ is critical to the maintenance of the fibrotic capsule, characterized in tumors such as Pancreatic Ductal Adeno Carcinoma (PDAC); this fibrosis is believed to limit access and effectiveness of standard of care chemotherapy
- NIS793 is a potential first-in-class neutralizing antibody specific for TGFβ
- NIS793 demonstrates compelling preclinical evidence, target engagement and acceptable safety profile in early clinical studies
- daNIS clinical trial program initiated, focused on role of NIS793, in combination with chemotherapy, in 1L PDAC (daNIS-2) and 2L CRC (daNIS-3)
- FDA granted orphan drug designation NIS793 in PDAC in July 2021
- Global regulatory submissions could occur as early as 2025
- Multi-blockbuster peak sales potential in 1L pancreatic cancer and in CRC
- US/EU: Patent on composition of matter (2032/2032)\(^2\)

---

1. GLOBOCAN 2020  2. Patent term extensions and regulatory-based exclusivities are possible
Pancreatic Ductal Adenocarcinoma (PDAC): One of the worst prognoses of all cancers

Pancreatic cancer is one of the leading causes of cancer death due to poor prognosis and limited treatment options

Majority of patients are diagnosed with metastatic disease with the lowest rate of survival amongst all major cancers\(^2\)
- Five-year survival for metastatic PDAC ~3\(^\%\)\(^1\)

Chemotherapy remains standard of care for PDAC with few to no new treatment approvals in 10+years

Outcomes across tumor types have improved significantly since the 1970s, but pancreatic remains among the deadliest\(^3\)

---

1. Globocan database (2020 data). Available at: https://gco.iarc.fr/today  
2. Pancreatic Cancer UK. Pancreatic Cancer Statistics  
3. McKinsey & Company
NIS793: First-in-class TGFβ with potent and specific inhibition of all TGF isoforms

Inhibition of TGFβ has opportunity to:
- **Reduce** the formation of the fibrotic capsule that limits the activity of chemotherapy
- **Restore** endogenous anti-tumor immunity
- **Reduce** tumor growth, angiogenesis, and metastasis

**NIS793:**
- **Saturates** binding of all TGFβ isoforms in patients
- **Optimized** to target TGFβ signaling in the tumor itself, the tumor microenvironment, as well as immune cell matrix
- **Enables flexibility** in combining with multiple modalities

---

Bauer TM, et al. Phase 1b study of the anti-TGF-β monoclonal antibody (mAb) NIS793 combined with spartalizumab (PDR001), a PD-1 inhibitor, in patients (pts) with advanced solid tumors. Oral presentation at: ASCO Annual Meeting; June 4, 2021

---

**NIS793, a first-in-class TGFβ inhibitor**

<table>
<thead>
<tr>
<th>NIS793</th>
<th>177 Lu-PSMA-617</th>
<th>Kisqali®</th>
<th>Sabatolimab</th>
<th>JDQ443</th>
<th>TNO155</th>
<th>T-Charge™</th>
<th>Scemblix®</th>
<th>NIS793</th>
</tr>
</thead>
</table>

Bauer TM, et al. Phase 1b study of the anti-TGF-β monoclonal antibody (mAb) NIS793 combined with spartalizumab (PDR001), a PD-1 inhibitor, in patients (pts) with advanced solid tumors. Oral presentation at: ASCO Annual Meeting; June 4, 2021

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TGFβ-blockade halts fibrosis development in models of cancer

In animal models of PDAC (left panel):
- Anti-TGFβ reduces fibrosis in animal models of cancer
- Anti-TGFβ in combination with gemcitabine/nab-paclitaxel demonstrated synergistic reduction in tumor volume in a mouse model of pancreatic cancer
- In the same mouse-model, the combination extended survival

In the FIH study:
- Inhibition of TGFβ signaling shown in peripheral blood and tumor tissue
- Free TGFβ levels were reduced to undetectable levels at all NIS793 doses tested
- In paired tumor biopsies, NIS793 showed inhibition of the TGFβ signaling pathway by a reduced expression of PMEPA1, a known TGFβ signaling target

Grauel AL et al, Nat Commun 2020
daNIS-2 Ph3 study of NIS793 + SOC in 1L pancreatic cancer

**daNIS-2 currently enrolling, expected completion early 2026**

- Metastatic pancreatic ductal adenocarcinoma (PDAC), not amenable for curative surgery
- No prior treatment in metastatic setting (1L treatment)
- ECOG PS 0-1

### daNIS-2 study design

- Safety run in N = 10 (1:1 R)
- N=480

#### daNIS-2 Ph3 study of NIS793 + SOC in 1L pancreatic cancer

**Treatment arms:**
- NIS793 + gemcitabine + nab-paclitaxel
- Placebo + gemcitabine + nab-paclitaxel

**Primary endpoint:**
- OS

**Secondary endpoints:**
- Efficacy: PFS, ORR, DCR, TTR, DOR (per RECIST1.1 by investigator)
- Safety and tolerability
- Health-related QOL
- PK and immunogenicity

---

**daNIS clinical trial program underway**

**daNIS-1** (n=156) NCT04390763
Ph2 of NIS793 ± PD1 + SOC1 in 1L mPDAC
- Testing hypothesis of addition of PD1 in PDAC
- Estimated completion: early 2023

**daNIS-3** (n=190) NCT04952753
Ph2 of NIS793 + bevacizumab + chemotherapy2 in 2L MSS mCRC
- Testing hypothesis of NIS793 + chemo in additional tumor type with fibrotic morphology
- Estimated completion: late 2023

---

**Gemcitabine + nab-paclitaxel** Modified FOLFOX6 or FOLFIRI.
NIBR and Technology Platforms
NIBR discovers and develops medicines across a broad range of disease areas with an increasingly focused portfolio of projects.
NIBR deploys a technology-forward approach to unlock therapeutic opportunities across five platforms

- **Discovery Chemistry**
  - Entresto | HFrEF

- **Biotherapeutics**
  - Leqvio | CVRR

- **Stem-Progenitor Cell Therapy**
  - Kymriah | B-ALL

- **Viral Gene Therapy**
  - Zolgensma | SMA

- **Radioligand Therapy**
  - Lutathera | NET

Crespo-Jara A. et al., Clinical Nuclear Medicine, 2016; PDB 2ffl, 2f8s, 1u04.
Chemistry platform unlocks new opportunities to address undruggable targets

Exploiting allostery to overcome drug resistance

- BCR-ABL1
- Myristoyl pocket binding to inhibit ABL1 kinase
- ABL001 (Scemblix)
- CML patients not responding to other tyrosine kinase inhibitors

Next generation intra-molecular glue

- SHP2
- Potent and highly selective conformational restriction
- TNO155
- Cancer: Lung, Head/Neck

Mapping ligandable sites across the proteome

- Protein with mapped cysteine residues
- Covalent drug discovery
- Identification and prosecution of high value targets
We continue to innovate on small molecules while building strong position in new technology platforms

<table>
<thead>
<tr>
<th>Key focus</th>
<th>TPD (Discovery Chemistry)</th>
<th>RLT</th>
<th>Gene</th>
<th>Cell</th>
<th>xRNA&lt;sup&gt;1&lt;/sup&gt; (Biotherapeutics)</th>
</tr>
</thead>
<tbody>
<tr>
<td># of projects&lt;sup&gt;2&lt;/sup&gt;</td>
<td>12</td>
<td>12</td>
<td>22</td>
<td>15</td>
<td>9</td>
</tr>
</tbody>
</table>

Source: Novartis early pipeline as of November 2021. Projects are active NIBR portfolio (excludes GDD pipeline); Early-stage NME are post development candidate milestone. 1.xRNA includes RNA targeting LMWs, ASOs, sRNA, mRNA cancer vaccines. 2. Exploratory to Ph1/2
**Targeted Protein Degradation**
A new science of therapeutics and pharmacology

**TPD platform overview**
- Target degradation to achieve therapeutic benefit
- TPD reflects induced proximity of a target and a ubiquitin ligase by a molecular glue or bifunctional degrader
- Enterprise scale investment in TPD innovation platforms drives glue discovery, chemical libraries and structural insights
- FIC potential for multiple glue and bifunctional degraders of previously undruggable targets

**Two distinct classes of Degrader Molecules**

- **Two distinct classes of Degrader Molecules**

**Bifunctional degraders**

- Target protein
- Small molecule
- Degradation complex
- Degraded protein

**Molecular glue degraders**

- Target protein
- Small molecule
- Degradation complex

---

**FIC** – First In Class
Novartis is enhancing a strong position in TPD with external partnerships

Tunable and selective platform to generate novel and TPD drugs

Next-generation targeted protein degradation
Proprietary covalent warhead induces target unfolding

Favorable pharmacology
Compatible with oral delivery and CNS exposure

License and collaboration agreement
Signed to Dunad’s covalent degrader platform and other technologies to develop and commercialize oncologic and other therapeutics specific for certain protein targets

High-throughput discovery of novel glue degraders
Collaboration to access a molecular glue discovery library

62+ targets screened with 10K+ library in CRBN Reverse-MAPPIT assay

Detects small molecule induced protein-protein interactions

Reverse-MAPIT

NEK7-CRBN recruitment screen at Orionis
### NIBR TPD and glues pipeline covers a wide range of indications

<table>
<thead>
<tr>
<th>Indication</th>
<th>Exploratory</th>
<th>Discovery</th>
<th>Optimization</th>
<th>Pre-clinical</th>
<th>Phase 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immuno-oncology</td>
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<tr>
<td>Immuno-oncology</td>
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<tr>
<td>Inflammation</td>
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<tr>
<td>Blood diseases</td>
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<tr>
<td>Immuno-oncology</td>
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<tr>
<td>Ovarian cancer</td>
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<tr>
<td>Breast cancer</td>
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<tr>
<td>Huntington’s</td>
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<tr>
<td>AML</td>
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<tr>
<td>Solid tumors</td>
<td></td>
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<tr>
<td>Ovarian cancer</td>
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<tr>
<td>Lung cancer</td>
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</tr>
</tbody>
</table>

Inter / Intra-molecular glues

Bi-functional degraders
Novartis is the only large pharma with significant homegrown TPD pipeline

TPD pipelines by originator

TPD pipelines by therapy area

Novartis pipeline as of November 2021, competitor pipelines as of March 2021
RLT is a priority modality for the oncology portfolio

Key commercial assets

Targeted Therapy

Radioligand Therapy

Cell & Gene

Differentiated Immunotherapy
Further enhancing our position in RLT

Expanding the indication space

- Neuroendocrine tumors and other solid tumors (SSTR and GRPR)
- Glioblastoma
- Breast cancer

Rapid drug design

- Enhancing precision targeting
  - Enhanced targeting via LMW and peptides
  - New linker chemistries

Improve target understanding, durability, localization, and potency
### External partnerships help sustain Novartis’ strong position in RLT

<table>
<thead>
<tr>
<th>Priority Area</th>
<th>Partner</th>
<th>Deal / Collaboration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combinations</td>
<td>artios</td>
<td>License and collaboration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DDR screening and identification of combination therapies</td>
</tr>
<tr>
<td>Targeting ligands</td>
<td>PeptiDream</td>
<td>Partnership</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Macrocyclic/constrained peptides generated with PeptiDream’s proprietary platform for RLT and peptide-drug-conjugate use</td>
</tr>
<tr>
<td>Targeting biologics</td>
<td>ADIMAB</td>
<td>Collaborations</td>
</tr>
<tr>
<td></td>
<td>AdCellera</td>
<td>Discovery and optimization of biologics against priority Novartis targets</td>
</tr>
</tbody>
</table>

DDR – DNA Damage Response
# Growing RLT research pipeline

## Potential to address a range of solid tumors

<table>
<thead>
<tr>
<th>Product</th>
<th>Disease (target)</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Filing</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{177}$Lu PSMA-617</td>
<td>Prostate cancer (PSMA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FDA and EMA submission complete</td>
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<tr>
<td>$^{68}$Ga PSMA-11</td>
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<td></td>
<td></td>
<td>Ph3 PSMFore study recruiting</td>
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<tr>
<td>$^{225}$Ac PSMA-617</td>
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<td></td>
<td></td>
<td></td>
<td>Ph3 PSMaddition study recruiting</td>
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<tr>
<td>$^{225}$Ac PSMA-R2</td>
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<td></td>
<td></td>
<td></td>
<td>nmCRPC under evaluation</td>
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<tr>
<td>$^{68}$Ga PSMA-R2</td>
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<td></td>
<td></td>
<td></td>
<td>BCR under evaluation</td>
</tr>
<tr>
<td>$^{177}$Lu-Dotatate</td>
<td>Neuroendocrine tumors (SSTR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FDA and EMA submissions complete</td>
</tr>
<tr>
<td>$^{177}$Lu NeoB</td>
<td>Multiple solid tumors^1 (GRPR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ph1 study recruiting</td>
</tr>
<tr>
<td>$^{177}$Lu FF-10158</td>
<td>Glioblastoma (integrin alphavbeta 3/5)</td>
<td></td>
<td></td>
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<td></td>
<td>Study planned upon imaging results</td>
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<tr>
<td>$^{68}$Ga FF-10158</td>
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<td></td>
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<td>Ph1 study recruiting</td>
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<td>FAPi</td>
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<td></td>
<td></td>
<td>Deal closed with SOFIE Biosciences Q1 2021</td>
</tr>
<tr>
<td>Other (preclinical)</td>
<td>Additional targets</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Targets under investigation</td>
</tr>
</tbody>
</table>

1. Breast cancer, GIST, GBM, neuroblastoma, ovarian, head & neck, esophageal

---

![Therapeutic and Imaging/Diagnostic Visualization](image-url)

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*NOVARTIS | Reimagining Medicine*
Our gene therapy platform innovates in three core areas

**Natural or engineered gene transfer**

- Direct gene replacement (Zolgensma and CPK850)
- Deliver novel cargos (e.g. anti-sense oligonucleotides and anti-bodies)

**AAV Tropism**

- Antibody targeting
- Endosomal pathway
- Receptor

**Switchable gene expression**

- Switchable expression of transgene
- Machine learning
- Library synthesis
- Selection
- Sequencing

**Capsid evolution for optimal tropism**

**Switchable expression of transgene**
## Beyond our internal pipeline, acquisitions and partnerships consolidate our position in viral gene therapies

<table>
<thead>
<tr>
<th>Priority Area</th>
<th>Partner</th>
<th>Deal / Collaboration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ocular Gene Therapies</strong></td>
<td><strong>DYNO THERAPEUTICS</strong></td>
<td><strong>License and collaboration</strong> using multi-cycle AI-driven optimization of AAV capsids for ocular delivery</td>
</tr>
<tr>
<td></td>
<td><strong>vedere</strong></td>
<td><strong>Acquisition</strong> of optogenetics gene therapy programs, novel AAV capsids, and licenses to optogenetics intellectual property</td>
</tr>
<tr>
<td></td>
<td><strong>ARCTOS medical</strong></td>
<td><strong>Acquisition</strong> of optogenetics-based technology and one pre-clinical optogenetic AAV gene therapy program in new MOA</td>
</tr>
<tr>
<td><strong>Neuroscience Gene Therapies</strong></td>
<td><strong>Sangamo Therapeutics</strong></td>
<td><strong>Collaboration and license</strong> to develop gene regulation therapies for three neurodevelopmental targets</td>
</tr>
</tbody>
</table>
AAV gene therapy for inherited retinal dystrophy due to mutations in RLBP1 gene

Retinitis Pigmentosa
- A progressive inherited retinal dystrophy that results in early night blindness, gradual loss of visual fields and visual acuity, leading to complete blindness in one’s 40s
- RLBP1 mutation cause a specific form of autosomal recessive retinitis pigmentosa
- Prevalence = 1:800,000 patients

Disease progression

CPK850
- AAV treatment that restores a functional copy of the RLBP1 gene to cells of the retina
- Ph1/2 clinical trial is ongoing

AAV treatment improves long-term dark adaptation in a mouse model of RLBP1 dystrophy
**Optogenetics as the basis for a gene-agnostic AAV treatment for blindness**

**Optogenetic Gene Therapy**
- Delivers a light sensitive protein to surviving cells of a degenerating retina
- Treats Inherited Retinal Dystrophy (IRD) patients agnostic of the genetic cause of disease (may be caused by mutations in over 200 different genes)
- May benefit macular degeneration patients with geographic regions of atrophy and surviving inner retinal cells
- Recent acquisitions position Novartis for leadership in the optogenetics space
**Novartis gene therapy research pipeline covers multiple disease areas and indications**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Exploratory</th>
<th>Discovery</th>
<th>Optimization</th>
<th>Pre-clinical</th>
<th>Phase 1/2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinitis Pigmentosa (CPK850)</td>
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<tr>
<td>Parkinson’s Disease</td>
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<tr>
<td>Autism spectrum disorder (4)</td>
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<tr>
<td>Alzheimer’s Disease</td>
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<tr>
<td>Neurodevelopmental target</td>
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<tr>
<td>Sickle Cell Disease</td>
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<tr>
<td>Respiratory target</td>
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<tr>
<td>Enzyme replacement therapy</td>
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<tr>
<td>Neuromuscular target 1</td>
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<tr>
<td>Neuromuscular target 2</td>
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<tr>
<td>Amyotrophic Lateral Sclerosis (ALS)</td>
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</tr>
</tbody>
</table>

**Disease Areas**
- Ophthalmology
- Neuroscience
- Disease Area X
- Musculoskeletal
**T-Charge™: A redesigned internal CAR-T technology platform**

**Minimal ex vivo culture to maximize in vivo expansion**

- **Apheresis**
- **Transduction**

  - Adoptive transfer

  - In-vivo expansion

- **T-Charge manufacturing process time will be less than 2 days**
- **With T-Charge, CAR-T cells can expand within their natural environment when infused into the patient**
- **10-50-fold fewer CAR-T cells infused compared to existing CAR-T therapies**

**T-Charge preserves T cell “stemness,” an important T cell characteristic closely tied to its therapeutic potential**

**Flow cytometry shows:**

- **T-Charge retains naïve / Tscm cells (CD45RO-/CCR7+)**
- **In contrast, the traditionally generated product consists mainly of central memory T cells (Tcm) (CD45RO+/CCR7+)**
Exploring new approaches in RNA therapeutics

Small interfering RNA to inhibit translation of PCSK9 (cardiovascular disease) - Inclisiran

Antisense therapy to lower lipoprotein(a) (cardiovascular disease) - Pelacarsen

Tissue targeted siRNA ex-hepatocytes

mRNA cancer vaccine
Appendix
Respiratory & Allergy
Our Respiratory & Allergy strategy is focused on areas of high unmet need, with a strong mid and late-stage pipeline

Respiratory & Allergy strategy

- Drive innovation in specialty asthma via CSJ117 anti-TSLP inhaled monotherapy as potential 1st inhaled biologic
- Deliver life-altering improvements for COPD patients, initially with icenticaftor’s CFTR potentiation, complemented by CSJ117 and early-stage assets
- Become food allergy leader by transforming SoC anaphylaxis avoidance to proactive treatment, enabling patients and families to live free from fear with ligelizumab and supported by pipeline/LCM
- Address life-threatening sub-specialty respiratory diseases, e.g., fibrotic lung disease, capitalizing on understanding of complex pathobiology and a diverse array of assets/MoAs

Assets highlighted today:
CSJ117, icenticaftor

<table>
<thead>
<tr>
<th>Compound (indication)</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Registration</th>
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Disease area

- Asthma / COPD
- Allergy
- Sub-specialty Resp

Note: ligelizumab food allergy content covered in the context of the IHD presentation
Note: bars in gantt chart indicate current phase of development.
Agenda
Speakers
Novartis Strategy and Growth Story
Cardiovascular and Renal
Immunology, Hepatology & Dermatology
Neuroscience
Oncology
NIBR and Technology Platforms
Appendix
Respiratory & Allergy
Submission schedules
References

Key highlights

- **40% of asthma patients uncontrolled** despite maximum standard of care; biologic penetration low at 4% and limited to T2-high population
- CSJ117 **binds with high affinity to human TSLP**, a key upstream cytokine in the asthma inflammatory cascade
- Potential to become the **first inhaled biologic directly targeting airways**, at the site of TSLP expression for a broad patient population in asthma
- **TSLP mechanism proven** to reduce exacerbations in T2-high and T2-low patients
- CSJ117 PoC study showed **reduction in airway inflammation**
- **Asthma Ph2b dose range** finding and safety extension studies ongoing; initiation of Ph3 program expected in 2023.
- In parallel development for **severe COPD**. Ph2 PoC study is recruiting. Readout expected in 2023
- **US/EU**: Patent on composition of matter (2036/2036)¹

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1. Patent term extensions and regulatory-based exclusivities are possible

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CSJ117

**Inhaled TSLP inhibitor**

**Phase 2**
On track to be first inhaled biologic, CSJ117 has the potential to transform severe asthma & COPD treatment paradigms

CSJ117 acts on upstream TSLP target in inflammation pathway
Potential to be first inhaled Bx directly targeting airways, at the site of TSLP expression
Convenient inhaled administration for a broad patient population (both T2-high and T2-low)

Asthma
- In asthma, 40% of the >339m patients have moderate-to-severe disease and suffer daily from the impact of being uncontrolled despite maximal standard of care
- Only 4% of the severe asthma patients have access to the currently approved injectable Bx that require phenotyping and are limited to allergic and eosinophilic diseases
- No approved Bx treatment for the T2-low asthma population (up to 50% of patients)

COPD
- One of the leading causes of mortality and healthcare burden, including significant disability adjusted life-years lost
- Current therapies (inhaled bronchodilators and corticosteroids) may improve symptoms, yet many patients remain symptomatic and at risk of exacerbations
- No approved Bx treatment

**TSLP is an upstream mediator of asthma, triggering inflammation via T2 and non-T2 pathways**

![Diagram of the immune system and asthma](image)

- **Allergens, pollutants, pathogens in contact with epithelium**
- **TSLP**
  - **T2 pathway**:
    - B cell differentiation and IgE release
    - Mast cell degranulation
    - Eosinophil migration
    - Neutrophil migration
    - IL-4, IL-5, IL-13, IL-17, IL-9
  - **Non-T2 pathway**:
    - IL, interleukin; TSLP, thymic stromal lymphopoietin.


---

**References**

- IL, interleukin; TSLP, thymic stromal lymphopoietin.
CSJ117 is an inhaled anti-TSLP antibody fragment which inhibits both T2 and non-T2 mediated inflammation

*Note: Asthma airway improvements observed in Ph2a proof-of-concept (PoC) study: NCT03138811. IL, interleukin; TSLP, thymic stromal lymphopoietin.


Inhaled CSJ117 (anti-TSLP)↓↓

T2 pathway↑↓

Non-T2 pathway↑↓

Immune cell activation and release of mediators:
- IL-4, IL-5, IL-13, IL-17, IL-9

Allergens, pollutants, pathogens in contact with epithelium

Reduced:
- Airway damage, bronchoconstriction, mucus, cough, exacerbation

Asthmatic airway

Asthmatic airway improved with CSJ117*
In Ph2a POC study, CSJ117 improved lung function compared with placebo

Arithmetic mean (+/− SE) of % decrease in FEV\textsubscript{1} over a 7-hour period following AIC

[Graph showing improvement in lung function]

Ph2a POC study data show:

- CSJ117 reduced allergen induced bronchoconstriction in adult pts with mild asthma
- Good tolerability and safety profile

Ph2b dose range finding study is evaluating 5 doses of CSJ117 in severe asthma pts

* p<0.05 significant difference between CSJ117 and placebo; data presented as mean ± SE. AIC, allergen inhalation challenge; AUC, area under the curve; EAR, early asthmatic response (hours 0-2); FEV\textsubscript{1}, forced expiratory volume in 1s. LAR, late asthmatic response; PBO, placebo; SCR, screening; SE, standard error. 1. Gauvreau GM et al. 2020; poster presented at ERS International Congress 2020
Asthma Ph2b and COPD POC studies are ongoing with expected readouts in 2023

### Market potential

<table>
<thead>
<tr>
<th>Indication</th>
<th>Asset potential</th>
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<tbody>
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<td>Asthma</td>
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### Addressable patients

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1. Approximate figures; Source: Novartis internal forecast for G7 countries
2. Total addressable population currently uncontrolled on relevant SoC.

### Upcoming milestones for development program

- **Asthma**
  - Initiation of Ph3 program expected 2023
- **COPD**
  - Read-out of Ph2 expected 2023

---

1. Asthma Ph2b and COPD POC studies are ongoing with expected readouts in 2023.
**Key highlights**

- **3.8m COPD patients** in G6 with majority uncontrolled despite inhaled therapies

- **Smoking leads to CFTR dysfunction** which is associated with COPD pathology, particularly in presence of chronic bronchitis

- By potentiating CFTR ion channels across various cell types, icenticaftor targets reductions in systemic inflammation, bacterial colonization and airway disease with potential for meaningful symptom improvements

- **Icenticaftor improved CFTR function, inflammation, lung function, and bacterial colonization** in a COPD POC study

- Recruitment to **Ph2b dose range finding study** has recently completed. Ph3 initiation targeted H1 2023

- Parallel **PoC study in bronchiectasis** ongoing

- **US/EU**: Patent on compound (2031/2031)
Icenticaftor represents a novel approach to COPD, with potential
to deliver life-altering symptom improvements

Unmet needs in COPD are large and neglected

- COPD is the 3rd leading cause of death worldwide\(^1\)
- COPD causes high morbidity and mortality and results in
  significant healthcare costs\(^2-5\)
- Many COPD patients with CB remain symptomatic and
  have exacerbations despite inhaled therapies\(^6\)
- Cough, sputum and shortness of breath are the most
  common/persistent symptoms affecting quality of life\(^7,8\)

Potential first to market blockbuster

- Only one new drug class has been approved
to treat COPD in the last decades and few new
entrants are anticipated beyond repurposed
asthma biologics
- Ph2b dose range finding study has completed
enrolment with results expected in H1 2022\(^9\)
- Given the multi-system efficacy of CFTR
  potentiation in CF\(^10\), multiple lifecycle
  opportunities are in scope
- A parallel PoC study in bronchiectasis is
  ongoing\(^11\)

---


CF: Cystic Fibrosis; CB: Chronic Bronchitis; PoC: Proof of Concept.
Icenticaftor, an oral CFTR potentiator, targets reductions in systemic inflammation, bacterial colonization & airway disease

**CFTR potentiation:** correction of acquired CFTR impairment across various cell types in COPD patients

Targeting reductions in systemic inflammation, bacterial colonization and airway disease

---

**References**

Icenticaftor improved CFTR function, inflammation, lung function, and bacterial colonization in COPD PoC study

Systemic CFTR function (sweat chloride)

Lung function (FEV₁)

Systemic inflammation (reduced fibrinogen)

Bacterial colonization

Icenticaftor, a novel oral CFTR potentiator, represents a potentially transformational approach to COPD

**Cell health**

CFTR function is disrupted in COPD

Icenticaftor potentiates CFTR in various cell types¹,²

**Lung health**

By potentiating CFTR ion channels across various cell types, icenticaftor targets reductions in systemic inflammation, bacterial colonization and airway disease

**Patient health**

Icenticaftor aims to deliver life-altering symptom improvements in COPD patients with chronic bronchitis

---

**Icenticaftor targets COPD and bronchiectasis indications with large market potential**

**Market potential**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Asset potential</th>
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<tbody>
<tr>
<td>COPD</td>
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<tr>
<td>Bronchiectasis</td>
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<tr>
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<td>○○○○ &gt;USD 2bn</td>
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**Addressable patients**

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**Upcoming milestones for development program**

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</table>

**COPD**

Ph2b dose range finding study has completed enrolment with results expected in H1 2022. Ph3 program initiation targeted H1 2023

**Bronchiectasis**

PoC Study ongoing

COPD: Chronic Obstructive Pulmonary Disease; PoC: Proof of Concept.  
1Approximate figures; Source: Novartis internal forecast for G6 countries.  
2Total addressable population currently uncontrolled on relevant SoC.
# Novartis submission schedule

New Molecular Entities: Lead and supplementary indications

## Lead Indications

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<td>NSCLC</td>
<td>LCM</td>
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<td>2024</td>
<td>fmiclizumab</td>
<td>ANCA-GN</td>
<td>LCM</td>
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<tr>
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<td>romelizumab</td>
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<td>&gt;2026</td>
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## New Indications

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1. Filing opportunity in 2022 / 2023, based on PFS and/or OS outcomes from a dual approach based on parallel Phase 2 and Phase 3 trials.
### Novartis submission schedule

**Supplementary indications for existing brands**

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  Iridal
  L368 | canakinumab
  AN2365
  Adcyvax NGLC
  L369 | Adalimumab
  AN2806
  L368 | Afibriccept
  BIBF6720
  L369 | **Brolucizumab**
  BIBF6720
  L369 |
| **Cosentyx**
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  secukinumab, AN1575
  Iridal
  L368 | **Cosentyx**
  secukinumab, AN1575
  Iridal
  L368 | **Cosentyx**
  secukinumab, AN1575
  Iridal
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  Iridal
  L368 |
| Bevacizumab
  AN1646
  L368 | Bevacizumab
  AN1646
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  AN1646
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  L368 | **Xolair**
  omalizumab, IGE025
  L368 | **Xolair**
  omalizumab, IGE025
  L368 |

1. Approved in US.  
2. 177Lu-dotatate in US.  
3. Kesimpta and Mayzent: pediatric study in multiple sclerosis run in conjunction (NEOS)
References
Immunology, Hepatology & Dermatology | Slide 4

42. Chandrashekar BS, et al. EADV 2020;P1279.
46. Blauvelt A et al. AAD 2021; Oral presentation; P27476.
51. Novartis data on file Clinical study report, CAIN457A2325.
57. ClinicalTrials.gov identifier: NCT03136861.