KRYSTEXXA® Immunomodulation Strategy and EULAR Data
Horizon Therapeutics plc

June 4, 2020
This presentation contains forward-looking statements, including, but not limited to, expected financial performance and operating results in future periods, including potential growth in net sales of certain of Horizon’s medicines; expected timing of clinical trials, studies and regulatory submissions; potential market opportunity for and benefits of Horizon’s medicines and medicine candidates; and business and other statements that are not historical facts. These forward-looking statements are based on Horizon’s current expectations and inherently involve significant risks and uncertainties. Actual results and the timing of events could differ materially from those anticipated in such forward-looking statements as a result of these risks and uncertainties, which include, without limitation, risks that Horizon’s actual future financial and operating results may differ from its expectations or goals; Horizon’s ability to grow net sales from existing medicines; risks relating to Horizon’s ability to successfully implement its business strategies; risks inherent in developing existing medicines for new indications; risks associated with regulatory approvals; risks in the ability to recruit, train and retain qualified personnel; competition, including potential generic competition; the ability to protect intellectual property and defend patents; regulatory obligations and oversight, including any changes in the legal and regulatory environment in which Horizon operates and those risks detailed from time-to-time under the caption "Risk Factors" and elsewhere in Horizon’s filings and reports with the SEC. Horizon undertakes no duty or obligation to update any forward-looking statements contained in this presentation as a result of new information.
Agenda

1. Introduction
   Tina Ventura
   Senior Vice President, Investor Relations, Horizon

2. KRYSTEXXA: A Trusted Medicine for Uncontrolled Gout
   Vikram Karnani
   Executive Vice President, Chief Commercial Officer, Horizon

3. KRYSTEXXA: Immunomodulation Strategy
   Jeffrey D. Kent, M.D., FACP, FACG
   Executive Vice President, Medical Affairs and Outcomes Research, Horizon

4. KRYSTEXXA: Immunomodulation Data
   John K. Botson, M.D., RPh, CCD
   Orthopedic Physicians Alaska;
   President of the Alaska Rheumatology Alliance
   Karim Richard Masri, M.D., RhMSUS
   Bon Secours Rheumatology Center, Richmond, VA

5. Q&A
Horizon: A Differentiated, High-Growth Biopharmaceutical Company

We are a leading, high-growth profitable biopharmaceutical company

- Focused on rare diseases, rheumatology, nephrology, ophthalmology and endocrinology
- Two high-growth drivers, TEPEZZA™ and KRYSTEXXA, with >$2B in combined peak U.S. annual net sales potential
- Strong track record executing our strategy of maximizing our key growth drivers while expanding our pipeline for sustainable growth

Delivering innovative therapies to patients

- Deep development expertise with proven track record
- Building a pipeline through M&A to support sustainable long-term growth

Generating high returns for shareholders

- Outperformed NBI for 1, 3 and 5 years
- Our prospects position us with a top-tier growth profile

(1) Horizon estimate.
Key Takeaways

*KRYSTEXXA with Immunomodulation Is Becoming the Standard Treatment for Patients with Uncontrolled Gout*

**KRYSTEXXA is a trusted medicine – the only approved biologic – for uncontrolled gout**
- Used for more than a decade in thousands of patients
- Can result in complete resolution in months

**Our KRYSTEXXA immunomodulation strategy is designed to maximize KRYSTEXXA’s benefit for patients and provide flexibility of choice for physicians**
- Immunomodulation has long been used to improve the response rate to biologic medicines
- Methotrexate is the immunomodulator of choice of rheumatologists; however, several other immunomodulators are also used with success to improve the response rate and safety profile of KRYSTEXXA\(^1\)

**Growing body of evidence supports KRYSTEXXA with immunomodulation; becoming the standard treatment**
- Results of trials and multiple real-world case series support use of KRYSTEXXA with methotrexate
- Additional trials and case series show benefit of other immunomodulators with KRYSTEXXA
- Number of patients studied using KRYSTEXXA with immunomodulation now approximates the number of patients that received KRYSTEXXA in the Phase 3 program

\(^1\) Horizon market research and IQVIA data.

Uncontrolled gout is chronic gout refractory (unresponsive) to conventional therapies.
KRYSTEXXA

A Trusted Medicine for Uncontrolled Gout
Gout: A Systemic Disease Often Associated with Multiple Negative Consequences

**Gout**

- Most common inflammatory arthritis\(^{(1)}\)
- Characterized by multiple comorbidities, including chronic kidney disease and hypertension
- Systemic disease; uric acid deposits can occur almost anywhere in the body

**Uncontrolled Gout**

- Chronic gout refractory (unresponsive) to conventional therapies
- Can result in decreased health-related quality of life and increased healthcare resource use\(^{(2)}\)
- Principle characteristics:
  - Elevated serum uric acid (sUA) levels
  - Acute gout flares; possible tophi
  - Bone erosions, loss of joint and limb functions; potential for chronic pain; more likely to suffer from CKD, diabetes and heart disease

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KRYSTEXXA: Used for a Decade in Thousands of Patients with Uncontrolled Gout

Approved in September 2010; relaunched by Horizon in 2016
• Only FDA-approved biologic to treat patients with uncontrolled gout

Studied in two Phase 3 clinical trials in 85 KRYSTEXXA patients
• Two replicate, randomized, double-blind placebo controlled trials
• Mean patient baseline sUA of 10mg/dL
• 42% of patients achieved a complete response rate\(^{(1)}\)
• 45% of patients achieved complete tophi resolution\(^{(2)}\)

Short course of therapy
• Finite course of therapy
• Once treatment is complete, patients can return to conventional therapy

Growing use by physicians
• Only FDA-approved option for physicians for treating uncontrolled gout
• >15,000 patients treated since approval

sUA: Serum uric acid.
Tophi: hard uric acid deposits.
\(^{(1)}\) Complete response defined as maintaining sUA <6 mg/dL for >80% of the time at 3 and 6 months.
\(^{(2)}\) Complete tophi resolution of at least 1 target tophus, with no new or progressive tophi, in 6 months.
KRSTEXXA: The Only Biologic Approved for Uncontrolled Gout

Differentiated Mechanism of Action

Before and After KRSTEXXA

Converts urate to water-soluble allantoin; Renal excretion of allantoin is up to 10x more efficient than excretion of uric acid

(1) Uncontrolled gout is chronic gout refractory (unresponsive) to conventional therapies.
Our Holistic Approach Maximizes the Value of Our Medicines for Patients

We DEEPLY UNDERSTAND the medicine, the disease and the market dynamics, investing in clinical data to advance the science.

We develop the right COMMERCIAL STRATEGY, TEAM AND INFRASTRUCTURE to support our patients and drive uptake.

We develop the right CLINICAL STRATEGY to improve physician understanding and clinical conviction to benefit more patients and optimize growth.

**KRYSTEXXA exemplifies our industry-leading holistic approach**

- **KRYSTEXXA** was an underperforming and undervalued asset at acquisition in Jan. 2016
- We transformed its growth trajectory through strong commercial execution, quintupling annual net sales in 4 years
- We are driving continued growth opportunities for **KRYSTEXXA**; projecting peak U.S. annual net sales of >$1B\(^{(1)}\)
- We are further maximizing **KRYSTEXXA** through our immunomodulation clinical strategy so more patients can benefit

\(^{(1)}\) Horizon estimate.
KRYSYETEXXA Immunomodulation Strategy

To Improve the KRYSYETEXXA Response Rate and Duration of Therapy and Allow Physicians the Flexibility to Choose Their Immunomodulator
Although KRYSTEXXA’s Response Rate in Phase 3 Trials Was Impressive...

• KRYSTEXXA’s 42 percent response rate was significant given that the uncontrolled gout patient population failed all prior therapies.

• Reduction of the body’s uric acid burden began with first infusion\(^{(2)}\).

• Patients had a rapid drop in serum uric acid (sUA) levels:
  – Within 24 hours following the first dose, mean uric acid levels for patients treated with KRYSTEXXA were 0.7 mg/dL (vs. 8.2 mg/dL with placebo)\(^{(3)(4)}\).

• Complete responders maintained sUA levels <6 mg/dL >80% of the time at Months 3 and 6 versus 0% for placebo (p <0.001).

Note: Complete response defined as maintaining sUA <6 mg/dL for >80% of the time at 3 and 6 months.

\(^{(1)}\) Pooled results of the intent-to-treat population receiving KRYSTEXXA 8 mg by IV infusion every 2 weeks; complete response defined as maintaining sUA <6 mg/dL for >80% of the time at 3 and 6 months.


\(^{(3)}\) KRYSTEXXA prescribing information.

...Significant Opportunity Exists to Improve KRYSTEXXA’s Response Rate with Immunomodulation
Allowing More Patients with Uncontrolled Gout to Benefit from the Medicine

Incomplete responders achieved a significant reduction in serum uric acid (sUA) for a mean of 7 weeks, allowing some clearance of the urate burden.

However, for incomplete responders, the response was not durable; the incomplete responders therefore did not meet the primary endpoint, which was achieving complete response(2)(3).

Note: Complete response defined as maintaining sUA <6 mg/dL for >80% of the time at 3 and 6 months.
(1) Pooled results of the intent-to-treat population receiving KRYSTEXXA 8 mg by IV infusion every 2 weeks; complete response defined as maintaining sUA <6 mg/dL for >80% of the time at 3 and 6 months.
(3) KRYSTEXXA prescribing information.
Anti-Drug Antibodies Can Lead to Loss of Response\(^{(1)}\)-(\(4\))

Some biologics can elicit an immune response in some individuals\(^{(1)}\)-(\(2\))

Anti-drug antibodies can develop; these anti-drug antibodies are common to biologic therapies\(^{(1)}\)-(\(2\))

It is often difficult to predict development of anti-drug antibodies\(^{(3)}\)-(\(4\))

Anti-drug antibodies can lead to an increased risk of infusion reactions\(^{(1)}\)-(\(4\))

Anti-drug antibodies may accelerate clearance of KRYSTEXXA from the circulation\(^{(5)}\)

Serum uric acid (sUA) levels >6 mg/dL often reflect the development of anti-drug antibodies to KRYSTEXXA

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(5) KRYSTEXXA prescribing information.
Horizon’s KRYSTEXXA Immunomodulation Strategy

Aiming to Solve the Problem of Loss of Response

**Objective**

Increase physician awareness of immunomodulation as an option to improve the rate of response, duration of therapy and safety profile of KRYSTEXXA so more patients can benefit

- Provides flexibility; allows physicians choice of immunomodulator and dose

**We are doing this by...**

- **Investing in research** with the MIRROR open-label and placebo-controlled randomized clinical trial to evaluate concomitant use of KRYSTEXXA with methotrexate
- **Supporting research and driving awareness** for the growing body of data that supports the concomitant use of KRYSTEXXA with immunomodulation
  - Methotrexate – the most commonly used immunomodulator by rheumatologists
  - Additional immunomodulators (leflunomide, MMF, azathioprine)

**Our strategy is resonating with physicians,** as evidenced by the increasing real-world adoption of immunomodulation

- Increasing percentage of physicians prescribing KRYSTEXXA with an immunomodulator; becoming the standard of treatment

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(1) Based on case studies or case reports that were not statistically powered to compare the efficacy or safety of KRYSTEXXA alone or with immunomodulation.

MMF: mycophenolate mofetil.

MIRROR: Immunomodulation program evaluating the use of KRYSTEXXA in combination with methotrexate to increase response rate. OL: Open-label trial; 14 patients; completed. RCT: Registrational randomized, placebo-controlled trial; 135-patients; ongoing.
Methotrexate is the most commonly used drug for systemic rheumatic diseases worldwide.

Methotrexate has been used extensively for >30 years by millions of patients worldwide for multiple conditions and has a well-established safety profile.

As an immunomodulator with KRYSTEXXA, methotrexate is used for a short, 6-month course of therapy.

Commonly used in 15mg weekly dose.
Results of KRYSTEXXA with MTX Studies Support Our Immunomodulation Strategy

**Response Rate**

79% - 100%

KRYSTEXXA + MTX

42%

KRYSTEXXA Phase 3

Additional positive immunomodulator data with leflunomide (LEF), mycophenolate mofetil (MMF) and azathioprine (AZA)

Response Rate of KRYSTEXXA with Methotrexate Dramatically Higher than KRYSTEXXA Alone

<table>
<thead>
<tr>
<th></th>
<th>KRYSTEXXA Alone</th>
<th>KRYSTEXXA plus Methotrexate</th>
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<tbody>
<tr>
<td>Response Rate</td>
<td></td>
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<tr>
<td>Phase 3 Clinical Trials</td>
<td>n=85 42%</td>
<td>n=14 79%</td>
</tr>
<tr>
<td>MIRROR OL (Open Label)</td>
<td>n=14 79%</td>
<td>n=10 80%</td>
</tr>
<tr>
<td>Albert Case Series  (Open Label)</td>
<td>n=10 80%</td>
<td>n=10 100%</td>
</tr>
<tr>
<td>Peterson Botson Case Series (Open-label)</td>
<td>n=10 100%</td>
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</tr>
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</table>

**Note:** Data from separate clinical trials may not be directly comparable due to differences in trial protocols, conditions and patient populations.


sUA: Serum uric acid.
Adoption of KRYSTEXXA with Immunomodulation Is Increasing Following Positive Data
Growing Body of Evidence of Concomitant Use Suggests the Standard Treatment in Uncontrolled Gout is Evolving

Dramatic increase in use of immunomodulation begins soon after first case series presented in Nov. 2018 showed a
100% response rate with use of KRYSTEXXA with methotrexate

AZA: azathioprine. MTX: methotrexate
ACR: American College of Rheumatology.
KRYSTEXXA Immunomodulation Study Results

Including New Data Presented at EULAR
Methotrexate: Botson Peterson Proof-of-Concept Case Series

Investigated If Using KRYSTEXXA with Methotrexate Could Improve Durability of Response

**Description**
- Real-world practice setting
- Enrolled sequentially
- No inclusion or exclusion criteria
- 3 infusion centers

**Dosing**
- KRYSTEXXA 8 mg biweekly
- Oral MTX 15 mg weekly and oral folic acid 1 mg daily 1 month prior to initial infusion and continued throughout treatment

**Efficacy**
- 10/10 patients completed full course of treatment

**Safety**
- 0/10 patients had infusion reactions
- 7/10 patients had ≥1 gout flare; no discontinuations due to flares

**Botson Peterson Case Series Results**

- 100% (10/10)

**Definition of Responders:**
Demonstrating >80% of pre-infusion sUA levels <6.0 mg/dL between Months 3 and 6

sUA: Serum uric acid.
MTX: Methotrexate.
Methotrexate: MIRROR Open-Label Trial

Investigated If Using KRYSTEXXA with Methotrexate Could Improve Durability of Response

Description
• Open-label efficacy and safety study

Dosing
• KRYSTEXXA 8 mg biweekly
• Oral MTX 15 mg weekly and oral folic acid 1 mg daily 4 weeks prior to initial infusion and continued throughout treatment

Efficacy
• 11/14 patients completed 6 months of treatment; the study continued to 12 months

Safety
• 14/14 patients tolerated MTX
• 12/14 experienced a gout flare; no discontinuations due to flares

sUA: Serum uric acid.
MTX: Methotrexate.
Methotrexate: Albert Case Series

**KRYSTEXXA with Oral or Subcutaneous Methotrexate**

**Description**
- Single community rheumatology practice
- Retrospective chart review

**Dosing**
- KRYSTEXXA 8 mg biweekly
- 9/10 patients received subcutaneous MTX 25 mg weekly before first KRYSTEXXA infusion; 1/10 patients received oral MTX 12.5 mg weekly after first KRYSTEXXA infusion

**Efficacy**
- 8/10 patients were considered responders

**Safety**
- No new safety concerns
- Gout flare occurred in 1 patient
- 1 patient had a mild infusion reaction and discontinued treatment

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**Albert Results**

<table>
<thead>
<tr>
<th>Response Rate</th>
<th>100%</th>
<th>80%</th>
<th>60%</th>
<th>40%</th>
<th>20%</th>
<th>0%</th>
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</thead>
</table>

**Primary Endpoint:**
Proportion of responders defined as ≥12 KRYSTEXXA infusions administered

sUA: Serum uric acid.
MTX: Methotrexate.
**Leflunomide: Masri Case Series**

*Evaluated Co-Therapy of KRYSTEXXA with Leflunomide in Patients with Uncontrolled Gout and Chronic Kidney Disease*

### Description
- Leflunomide: chosen due to its safety in chronic kidney disease patients without the need of dose titration
- Rheumatology practice
- Retrospective study

### Dosing
- KRYSTEXXA 8 mg biweekly
- Oral leflunomide 20 mg per day

### Efficacy
- 7/10 patients received ≥12 infusions

### Safety
- No new safety concerns
- 3 patients discontinued and were lost to follow-up, however, they had no infusion reactions
- 1 patient had three gout flares

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**Masri Results**

- **70%** (7/10)

**Primary Endpoint:**

Proportion of responders defined as ≥12 KRYSTEXXA infusions administered

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sUA: Serum uric acid.
Growing Body of Evidence Continues to Support Concomitant Immunomodulation with KRYSTEXXA

<table>
<thead>
<tr>
<th>Publication</th>
<th>% of responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berhanu AA, et al (1)</td>
<td>100% (1/1)</td>
</tr>
<tr>
<td>Freyne B (2)</td>
<td>100% (1/1)</td>
</tr>
<tr>
<td>Botson J, Peterson J (3)(4)</td>
<td>100% (10/10)</td>
</tr>
<tr>
<td>Albert J, et al (5)</td>
<td>80% (8/10)</td>
</tr>
<tr>
<td>Bessen MY, et al (6)</td>
<td>100% (7/7)</td>
</tr>
<tr>
<td>MIRROR (7)</td>
<td>79% (11/14)</td>
</tr>
<tr>
<td>Masri K, et al (8)</td>
<td>70% (7/10)</td>
</tr>
<tr>
<td>RECIPE (9)</td>
<td>(n=32)*</td>
</tr>
<tr>
<td>TRIPLE (10)</td>
<td>(n=12)*</td>
</tr>
</tbody>
</table>

### Cumulative Patients Studied Using Concomitant Immunomodulation with KRYSTEXXA

![Graph showing cumulative patients studied](image)

**Note:** None of these case studies or case reports were statistically powered to compare the efficacy or safety of KRYSTEXXA alone or with immunomodulation.

**Note:** The patient in the Freyne publication received both cyclosporine and MMF.


*Represents either completed trial for which data has not yet been disclosed (RECIPE) or ongoing trial (TRIPLE); complete data to be presented at a future date.

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(3) Botson J, Peterson J. Arthritis Rheumatol. 2018;70 (suppl 10).
(9) RECIPE: randomized controlled trial evaluating KRYSTEXXA with MMF.
(10) TRIPLE: ongoing open-label trial evaluating KRYSTEXXA with AZA.

Note: None of these case studies or case reports were statistically powered to compare the efficacy or safety of KRYSTEXXA alone or with immunomodulation.

Note: The patient in the Freyne publication received both cyclosporine and MMF.

Methotrexate: MIRROR RCT Underway to Potentially Expand Prescribing Information

Enrollment ~80 Percent Complete

Description
- Follows successful MIRROR open-label
- 135 patients (~80 percent enrolled)
- Following MIRROR RCT readout, potential to expand prescribing information

Dosing
- KRYSTEXXA 8 mg biweekly
- Oral MTX 15 mg weekly
- Oral folic acid 1 mg daily

MIRROR Randomized Clinical Trial Design

135 Patients Evaluated for 24 Weeks

- KRYSTEXXA + methotrexate (n=90)
  12 infusions: 1 every two weeks
- KRYSTEXXA + placebo (n=45)
  12 infusions: 1 every two weeks

Initiated Q2 2019; Data Readout Expected in 2021

Primary Endpoint at Week 24:
Proportion of Month 6 responders, defined as sUA <6 mg/dL for at least 80% of the time during Month 6

MTX: Methotrexate.
RCT: Randomized controlled trial.
Our Immunomodulation Strategy: One of KRYSTEXXA Growth Drivers

Uppside to Our Peak U.S. Annual Net Sales Expectations of >$1B\(^{(1)}\)

1. Growth in new and existing accounts
2. Accelerating nephrology growth
3. Growth in use of KRYSTEXXA plus immunomodulation

(1) Horizon estimate.
Key Takeaways

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