Novartis R&D and investor update

November 5, 2018
Disclaimer

This presentation contains forward-looking statements within the meaning of the United States Private Securities Litigation Reform Act of 1995, that can generally be identified by words such as “potential,” “expected,” “will,” “planned,” “pipeline,” “outlook,” “agreement to acquire,” or similar expressions, or by express or implied discussions regarding potential marketing approvals, new indications or labeling for the investigational or approved products described in this presentation, or regarding potential future revenues from such products, or regarding the proposed acquisition of Endocyte, Inc. (Endocyte) by Novartis including the potential outcome and expected timing for completion of the proposed acquisition, and the potential impact on Novartis of the proposed acquisition, including express or implied discussions regarding potential future sales or earnings of Novartis, and any potential strategic benefits, synergies or opportunities expected as a result of the proposed acquisition. You should not place undue reliance on these statements. Such forward-looking statements are based on our current beliefs and expectations regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that the investigational or approved products described in this presentation will be submitted or approved for sale or for any additional indications or labeling in any market, or at any particular time. Nor can there be any guarantee that such products will be commercially successful in the future. Neither can there be any guarantee that the acquisition described in this presentation will be completed, or that it will be completed as currently proposed, or at any particular time. There can be no guarantee that Novartis or any potential products that would be obtained with Endocyte will achieve any particular future financial results, or that Novartis will be able to realize any potential strategic benefits or opportunities as a result of the proposed acquisition. In particular, our expectations regarding such products matters could be affected by, among other things, the uncertainties inherent in research and development, including clinical trial results and additional analysis of existing clinical data; regulatory actions or delays or government regulation generally, including potential regulatory actions or delays with respect to the development of the products described in this presentation, as well as potential regulatory actions or delays relating to the completion of the potential acquisition described in this presentation; global trends toward health care cost containment, including government, payor and general public pricing and reimbursement pressures; our ability to obtain or maintain proprietary intellectual property protection; the particular prescribing preferences of physicians and patients; general political and economic conditions; safety, quality or manufacturing issues; the ability to obtain Endocyte stockholder approval and the satisfaction of the other conditions to the consummation of the proposed acquisition; the potential that the strategic benefits or opportunities expected to result from the proposed acquisition may not be realized or may take longer to realize than expected; the potential that the integration of Endocyte into Novartis subsequent to the closing of the proposed acquisition may not be successful, or may take longer to succeed than expected; potential adverse reactions to the proposed acquisition by customers, suppliers or strategic partners; dependence on key Endocyte personnel, customers and suppliers; uncertainties regarding actual or potential legal proceedings, including, among others, potential legal proceedings with respect to the proposed acquisition; potential or actual data security and data privacy breaches, or disruptions of our information technology systems, and other risks and factors referred to in Novartis AG's current Form 20-F on file with the US Securities and Exchange Commission. Novartis is providing the information in this presentation as of this date and does not undertake any obligation to update any forward-looking statements as a result of new information, future events or otherwise.

Additional Information and Where to Find It

This presentation may be deemed to be solicitation material in respect of the proposed acquisition of Endocyte by Novartis AG. In connection with the proposed acquisition, Endocyte filed a preliminary proxy statement with the SEC on October 31, 2018, and intends to file other relevant materials with the SEC, including Endocyte’s proxy statement in definitive form. Stockholders of Endocyte are urged to read these materials (including any amendments or supplements thereto) and all other relevant documents filed with the SEC when such documents become available, including Endocyte’s definitive proxy statement, because they will contain important information about the proposed acquisition. Investors and security holders are able to obtain the documents (once available) free of charge at the SEC’s web site, http://www.sec.gov, or from Endocyte by going to its investor relations web site at http://investor.endocyte.com/investor-relations. Participants in Solicitation

Novartis AG and its directors and executive officers, and Endocyte and its directors and executive officers, may be deemed to be participants in the solicitation of proxies from the holders of Endocyte shares of common stock in respect of the proposed acquisition. Information about the directors and executive officers of Novartis AG is set forth in the excerpts of Novartis AG’s Annual Report for 2017, which was furnished to the SEC on Form 6-K on January 24, 2018 and incorporated by reference into Novartis AG’s Annual Report on Form 20-F for the fiscal year ended December 31, 2017. Information about the directors and executive officers of Endocyte is set forth in the proxy statement for Endocyte’s 2018 Annual Meeting of Stockholders, which was filed with the SEC on March 23, 2018. Information regarding interests of Endocyte’s participants in the solicitation is set forth in Endocyte’s preliminary proxy statement relating to the proposed acquisition, and will be set forth in other materials to be filed with the SEC relating to the proposed acquisition, including Endocyte’s definitive proxy statement.
# Agenda

<table>
<thead>
<tr>
<th>Timing</th>
<th>Q&amp;A</th>
<th>Session</th>
<th>Presenters</th>
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</thead>
<tbody>
<tr>
<td>12:00 – 13:00</td>
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<td>Registration / light lunch</td>
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<tr>
<td>13:00</td>
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<td>Opening</td>
<td>Samir Shah</td>
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<tr>
<td>13:00 – 13:20</td>
<td>5 min</td>
<td>Pipeline, platforms</td>
<td>John Tsai</td>
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<tr>
<td>13:20 – 14:20</td>
<td>30 min</td>
<td>AveXis AVXS-101</td>
<td>Dave Lennon, Brian Kaspar</td>
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<tr>
<td>14:20 – 15:15</td>
<td>30 min</td>
<td>Oncology Radioligand therapies, ACZ885 in NSCLC, SEG101, BYL719</td>
<td>Liz Barrett, Samit Hirawat</td>
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<td>15:15 – 15:45</td>
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<td>Break</td>
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<tr>
<td>15:45 – 16:45</td>
<td>30 min</td>
<td>Upcoming launches (late-stage pipeline) QAW039, RTH258, BAF312, OMB157</td>
<td>John Tsai, Danny Bar Zohar, Paul Hudson</td>
</tr>
<tr>
<td>16:45 – 17:15</td>
<td>10 min</td>
<td>Near term value drivers Cosentyx®, Entresto®, Gilenya®</td>
<td>Paul Hudson, John Tsai</td>
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<tr>
<td>17:15 – 17:30</td>
<td>15 min</td>
<td>Q&amp;A session</td>
<td>Vas Narasimhan, Harry Kirsch, John Tsai, Paul Hudson, Liz Barrett</td>
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<tr>
<td>17:30</td>
<td></td>
<td>Cocktail</td>
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Highlights for today

- Leading pipeline with 26 potential blockbusters\(^1\)
- 60 major\(^2\) submissions planned 2019-2021
- Progressing advanced therapy platforms with 13 projects in development
- Deep Ph2 pipeline with emerging assets, including liver and kidney
- Maximizing our in-line brands with continuous new data flow
- Using data and digital technologies to strengthen the way we work

1. Individual assets with expected peak sales >USD 1bn across all indications  
Advancing a highly productive and valuable pipeline

<table>
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<tr>
<th>Scale</th>
<th>Value</th>
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<tr>
<td>200+</td>
<td>26</td>
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<tr>
<td>&gt;500</td>
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<tr>
<td>60</td>
<td>13</td>
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</tbody>
</table>

- **Projects in clinical development**: 200+
- **Ongoing clinical trials**: >500
- **Major submissions planned 2019-2021**: 60
- **Potential blockbusters in confirmatory development**: 26
- **Advanced platform therapies in clinical development; expected to enter the clinic in 2019**: 13

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1. Individual assets with expected peak sales >$1bn across all indications.
2. Across NIBR and GDD
Industry-leading on multiple metrics

#1
in value creation from advanced therapies

~USD 23bn
Highest pipeline value by sales 2018-24

~USD 95bn
Value creation 2018-24 from recently launched\(^1\) and pipeline products

Driving productivity using data and digital technologies

Transforming our operations through technology
Establishing a suite of innovative and advanced therapy platforms

- **Cell-based therapy**
  - Cancer cell
  - T-cell

- **CRISPR**

- **Gene therapy**

- **Covalent Binders**

- **mRNA**

- **Novel IO Rx Delivery**

- **Targeted Protein Degradation**

- **Radioligand therapy**

All trademarks are the property of their respective owners
Progressing gene, cell, and radioligand platforms with 13 therapies in development

Gene therapy

Cell therapy

Radioligand therapy

1. Gene therapy: 3 (AVXS-101, CGF166, CPK850)  
   Cell therapy: 6 (DLBCL 1st relapse, follicular lymphoma, DLBCL pembro combo, adult ALL, CLL, rr MM)  
   Radioligand: 4 (3 for prostate and one other)

2. The acquisition of Endocyte is subject to customary closing conditions, including receipt of regulatory approvals and Endocyte stockholders approval. Until closing, Endocyte will continue to operate as a separate and independent company.
# Building TA depth in Innovative Medicines

## Oncology
- **Kymriah**: New indications (Breast, Sickle Cell, NeET)
- **Alpelisib** (BYL719)
- **Crizanlizumab** (SEG101)
- **Lutathera**: NeET
- **ACZ885, INC280**: Lung

## Specialty Medicines

<table>
<thead>
<tr>
<th>Oncology</th>
<th>Cardio-Metabolic</th>
<th>IHD</th>
<th>Neuroscience</th>
<th>Ophthalmology</th>
<th>Respiratory</th>
<th>Biopharma</th>
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<tbody>
<tr>
<td>Entresto®</td>
<td>Cosentyx®</td>
<td>Aimovig®</td>
<td>Brolucizumab</td>
<td>Fevipiprant</td>
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<td>HFpEF</td>
<td>LCM</td>
<td>Migraine</td>
<td>(RTH258)</td>
<td>(QAW039)</td>
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<td>LHW090</td>
<td>Ligelizumab</td>
<td>Mayzent™</td>
<td>nAMD, DME</td>
<td>Asthma</td>
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<td>Hypertension</td>
<td>(QGE031)</td>
<td>(BAF312)</td>
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<td>QVM149</td>
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<td>LNP023</td>
<td>ZPL389</td>
<td>SPMS</td>
<td>Luxturna®</td>
<td>Asthma</td>
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<td>Renal Diseases</td>
<td>AD</td>
<td>Ofatumumab</td>
<td>Inherited retinal dystrophies</td>
<td>CSJ117</td>
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<td>LOU064</td>
<td>(OMB157)</td>
<td>UNR844</td>
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<td>MS</td>
<td>Presbyopia</td>
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<td></td>
<td>Tropifexor</td>
<td>AVXS-101</td>
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<td></td>
<td>(LJN452)</td>
<td>SMA</td>
<td>Dry eye</td>
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<td>LMI070</td>
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<td>SMA</td>
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<td>Transplant</td>
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<td>Neuropathic Pain</td>
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## Biopharma
- **Adalimumab**: In collaboration with Amgen
- **Infliximab**:
- **Pegfilgrastim**: LMI070, SMA

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Aimovig® is developed in collaboration with Amgen; Luxturna marketed ex-US
60 major\(^1\) submissions expected 2019-2021. 26 potential blockbusters\(^2\) in pipeline

Potential blockbusters

1. Submissions in US, Europe and Japan
2. Individual assets with expected peak sales >USD 1bn
3. Assets in confirmatory development
Endocyte assets not included

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\(^1\) Submissions in US, Europe and Japan
\(^2\) Individual assets with expected peak sales >USD 1bn
\(^3\) Including other potential indications
High, unmet medical need for effective treatment in NASH

153 million adults in the US suffer from nonalcoholic fatty liver disease (NAFLD)
25% of these people (38 million) will develop nonalcoholic steatohepatitis (NASH)
NASH is expected to be the leading cause of liver transplant in the US by 2020\(^3\)

Aiming to deliver best-in-class single and combination therapies for NASH patients

Working to build the broadest portfolio of combination products for NASH, to deliver benefits for patients

Tropifexor (LJN452) has the potential to be a backbone mechanism of action for combination therapies\(^1\)

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1. Clinical trials of tropifexor in combination with Allergan and Pfizer compounds in accordance with collaboration agreements with those companies. Clinical trials of tropifexor in combination with VAY785 conducted in accordance with collaboration and license agreement with Conatus Pharmaceuticals Inc. All trademarks are the property of their respective owners.
Renal a potential strategic pillar for the cardio-metabolic portfolio

High Unmet Need

- Major cause of death and risk factor for CV diseases\(^1\)
- High cost burden (US annual cost of dialysis: USD 42bn)
- No approved disease modifying treatment options in many conditions

Strong Strategic Fit

- Large renal market with significant growth potential (~USD 22bn in US in 2026\(^2\))
- Significant synergies between cardiovascular and renal diseases
- Potential for accelerated development pathways (e.g., surrogate marker)

Leading Renal Pipeline

- LNP023, oral alternative complement pathway inhibitor for rare renal diseases including IgA and Membranous Nephropathies, and C3 Glomerulopathy
- Nine projects specialty renal indications in pre-clinical development

\(^1\)Kidney International, Vol. 66 (2004), pp. 1310–1314; \(^2\)Evaluate Pharma
Maximizing in-line brands with major regulatory and clinical milestone in 2018

<table>
<thead>
<tr>
<th>Brand</th>
<th>Milestone</th>
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<tbody>
<tr>
<td>Aimovig®</td>
<td>US / EU approvals for migraine prevention</td>
</tr>
<tr>
<td>Cosentyx®</td>
<td>Ankylosing spondylitis submission in Japan</td>
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<tr>
<td>Entresto®</td>
<td>HFrEF: PIONEER-HF data to be presented at AHA</td>
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<td>HFrEF: TRANSITION demonstrated initiation of Entresto® shortly after stabilization of ADHF well tolerated</td>
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<tr>
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<td>HFrEF: PARAGON following interim analysis, study continue as planned with top-line results expected mid-2019</td>
</tr>
<tr>
<td>Gilenya®</td>
<td>Superiority vs. Copaxone® (ASSESS study); US approval &amp; CHMP positive opinion in pediatric indication</td>
</tr>
<tr>
<td>Kisqali®</td>
<td>MONALEESA 3 and 7 data added to US label</td>
</tr>
<tr>
<td>Kymriah®</td>
<td>DLBCL US/EU and pALL EU approval</td>
</tr>
<tr>
<td>Lucentis®</td>
<td>EU submission for retinopathy of prematurity</td>
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<tr>
<td>Lutathera®</td>
<td>US approval for NET</td>
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<tr>
<td>Tafinlar® +</td>
<td>US/EU/JP approval for adjuvant melanoma</td>
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<tr>
<td>Mekinist®</td>
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<tr>
<td>Biosimilars</td>
<td>EU approvals for adalimumab and infliximab, CHMP positive opinion for pegfilgrastim; US CRL for rituximab</td>
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</table>

Aimovig® is developed in collaboration with Amgen. Copaxone® is a registered trademark of Teva Pharmaceuticals LTD.
Strong commitment to integrating global health needs and access principles in R&D

Novartis Institute for Tropical Diseases

- Two NMEs (KAE609 and KAF156) in development for malaria with potential to address emerging resistance
- Discovery efforts targeting malaria, other parasitic and diarrheal diseases

Commitment to Malaria

- Five-year USD 100m investment targeting malaria in collaboration with external partners, such as the Medicines for Malaria Venture

Sickle Cell Disease Initiative

- Established new initiative targeting sickle cell disease (SCD) in Africa
- Partnered with selected governments
- Building on Novartis/Sandoz portfolio in SCD and strengthening disease education

Access Principles in R&D

- Commitment to identify opportunities within portfolio that better serve patients in low and low-middle income countries
- Commitment to incorporate considerations for LIC/LMIC in all development programs

1. Access Principles apply to how we research, develop and commercialize globally (though the focus of this slide is specifically R&D)
2. Low Income Countries / Low and Medium Income Countries
Conclusion

- Continuing our heritage of delivering breakthrough innovation
- Building a portfolio of advanced therapy platforms
- Advancing a pipeline of medicines addressing a high burden of disease
- Maximizing our in-line brands
- Driving R&D productivity to maximize pipeline potential
Appendix
Complement-mediated renal diseases are rare and affect young patients with often devastating outcomes

**IgA Nephropathy**
- ~125k patients in US; higher incidence in Asia Pacific; commonly diagnosed aged 20-40
- Clinical features include proteinuria, gross hematuria, fatigue and pain
- ~30% of patients with 1-2 g/day proteinuria progress to ESRD within 10 years
- No disease specific treatment options

**Membranous Nephropathy**
- ~84k patients in US; commonly diagnosed aged 40-60
- Most common cause of nephrotic syndrome in adults; edema common clinical feature
- ~30% of patients progressing to ESRD within 10 years
- No approved disease modifying therapies

**C3 Glomerulopathy**
- ~4k patients in US; commonly diagnosed in adolescents and young adults
- Clinical features include proteinuria, hematuria, nephrotic syndrome, fatigue
- ~50% of patients progressing to ESRD within 10 years; high rate of recurrence post-transplant
- No disease specific treatment options
### Planned filings 2018 to ≥ 2022

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<thead>
<tr>
<th>2018</th>
<th>2019</th>
<th>2020</th>
<th>2021</th>
<th>≥ 2022</th>
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<tr>
<td>BYL719® + fulv HR+, HER2+ postmenopausal adv. BIC 2nd line</td>
<td>INC280 NSCLC</td>
<td>AVXS-101 SMA Type 2/3</td>
<td>ABL001 CML® 3rd line</td>
<td>LJC242 Non-alcoholic steatohepatitis</td>
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<td>LCi699 Cushing’s disease</td>
<td>PDR001 + Tafinlar®+Mekinist® Metastatic BRAF V600L melanoma</td>
<td>QAW039 Asthma</td>
<td>QGE031 CSUCl®</td>
<td>BYM338 Non-alcoholic steatohepatitis</td>
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<td>RTH258 NMDK</td>
<td>SEG101 Sickle cell disease</td>
<td>Entresto® Post-acute myocardial infarction</td>
<td>ACZ285 1st Line NSCLC</td>
<td>CFZ533 Sjögren’s Syndrome</td>
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<td>LAM320 MDR® tuberculosis</td>
<td>Cosentyx® mAspA®</td>
<td>Cosentyx® Psa H24/17</td>
<td>ACZ285 2nd Line NSCLC</td>
<td>Cosentyx® AS H24/17</td>
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<td>Lucentis® RCP®</td>
<td>Entresto® Heart failure (PEF) 2</td>
<td>Jakav® Chronic GVHD 1</td>
<td>Kymriah ® r/r DLBCL in 1st relapse</td>
<td>Kymriah + pembrolizumab - r/r DLBCL</td>
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<td>Lucentis® Diabetic retinopathy</td>
<td>OMB157 Relapsing multiple sclerosis</td>
<td>Jakav® Acute GVHD 1</td>
<td>Kymriah® r/r Folicular Lymphoma</td>
<td>INC280 NSCLC (Egfr)</td>
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<td>QMF149 Asthma</td>
<td>RTH258 Diabetic macular edema</td>
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<td>Kisqali® HR+, HER2 (± BC) (adjuvant)</td>
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<td>QVM149 Asthma</td>
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<td>PDR001 combo Metastatic Melanoma</td>
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<td>Rydapt® AML® (FLt3 wild type)</td>
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<td></td>
<td></td>
<td>RTH258 Retinal vein occlusion</td>
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<td>VAY736 Primary Sjögren’s syndrome</td>
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<td>LA-EP2006 (pegfilgrastim, US) Chemotherapy-induced osteoporosis and others (same as originator)</td>
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1. Secondary prevention of cardiovascular events  
2. Diffuse large B-cell lymphoma  
3. Severe aplastic anemia  
4. Chronic myeloid leukemia  
5. Long-acting release  
6. Non-small cell lung cancer  
7. Neurovascular age-related macular degeneration  
8. Multi-drug resistant  
9. Breast cancer  
10. Retinopathy of prematurity  
11. Indolent Non-Hodgkin’s lymphoma  
12. Non-radiographic axial spondyloarthritis  
13. Preserved ejection fraction  
14. Graft-versus-host disease  
15. Neuroendocrine tumors  
16. Chronic spontaneous uveitis / chronic idiopathic uveitis  
17. Psoriatic arthritis head-to-head study versus adalimumab  
18. Non-alcoholic steatohepatitis  
19. Ankylosing spondylitis head-to-head study versus adalimumab  
20. Acute myeloid leukemia  
21. Chronic Obstructive Pulmonary Disease  
22. Secondary Progressive Multiple Sclerosis  
23. IV formulation Spinal Muscular Atrophy Type 1  
24. 1st line colorectal cancer / 1st line renal cell carcinoma  
25. IT formulation Spinal Muscular Atrophy Type 2/3  

**Combination abbreviations:**  
fulv fulvestrant  
tmx tamoxifen  
gsr goserelin  
NSAI Non-steroidal aromatase inhibitor  
Tal Tafinlar® (dabrafenib)  
Mok Mekinist® (trametinib)

**New molecule**  
**New indication**  
**New formulation**  
**Biosimilars**
**Pipeline of key projects in confirmatory development**

<table>
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<th>Early Clinical Trials</th>
<th>Registration Trials – Ph3 / Pivotal</th>
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<tr>
<td>AVXS-201 Not Syndrome</td>
<td>ABL001 DLL3 3rd line</td>
<td>AVXS-101 SMA Type 1</td>
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<td>KAF156 Malaria</td>
<td>ACZ885 2nd Line NSCLC</td>
<td>LAM320 MDR + tuberculosis</td>
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<td>VAY785&lt;sup&gt;5&lt;/sup&gt; Non-ocular mislecular neoplasms</td>
<td>VAY8730 Primary Spineylogn's syndrome</td>
<td>Lucentis Diabetic macular degeneration</td>
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<td>BYM338 Hip fracture recovery</td>
<td>AYX-V101 SMA Type 2/3</td>
<td>Lucentis Diabetic retinopathy</td>
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<td>LHW90/090 Resistant hypertension</td>
<td>BYL711 + fulv + HR, HER2 (adometastasal adv)</td>
<td>Lucentis ROP +</td>
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<td>CAD106 Alzheimer’s disease</td>
<td>ICX1200 NSCLC2</td>
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<td>ICX840 AS H2H</td>
<td>ACZ885 Sec. prev. CV events&lt;sup&gt;1&lt;/sup&gt;</td>
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<tr>
<td>CNP520 Alzheimer’s disease</td>
<td>Kymriah &lt;sup&gt;®&lt;/sup&gt; rF Lymphoma</td>
<td>Kiskali&lt;sup&gt;23&lt;/sup&gt; H7R + gsn/y/gsn NSAI + gsn H7R, HER2 (panmetastasal adv) or metastatic BC 1st line</td>
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<td>CSJ117 Severe Asthma</td>
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<td>Promacta&lt;sup&gt;®&lt;/sup&gt;/Revolada&lt;sup&gt;®&lt;/sup&gt; SAA&lt;sup&gt;®&lt;/sup&gt; 1st line</td>
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<tr>
<td>LOU64 Chronic spontaneous urticaria</td>
<td>ICX840 ALM&lt;sup&gt;®&lt;/sup&gt; (FL,T2, mild type)</td>
<td>FTY720 Pediatric multiple sclerosis</td>
</tr>
<tr>
<td>ECF843 Dry eye</td>
<td>Entresto&lt;sup&gt;®&lt;/sup&gt; Heart failure (PEF)&lt;sup&gt;11&lt;/sup&gt;</td>
<td>GP2017 (adalimumab) Arthritis, plaque psoriasis and others (same as originator)</td>
</tr>
<tr>
<td>EMA401 Peripheral neuropathic pain</td>
<td>Entresto&lt;sup&gt;®&lt;/sup&gt; Post-acute myocardial infarction</td>
<td>GP2013 (rituximab, US) Follicular lymphoma, DLBCL + and others (same as originator)</td>
</tr>
<tr>
<td>HDM201 Acute myeloid leukemia</td>
<td>Lyripl © AML&lt;sup&gt;®b&lt;/sup&gt;</td>
<td>LA-EP2006 (pegfilgrastim, US) Chemotherapy induced neutropenia and others (same as originator)</td>
</tr>
<tr>
<td>KAE609 Malaria</td>
<td>OXG301 CSU/CLIP</td>
<td>LA-EP2006 (pegfilgrastim, EU) Chemotherapy induced neutropenia and others (same as originator)</td>
</tr>
<tr>
<td>VAY736 Autoimmune Hepatitis</td>
<td>ACZ885 Acute GVHD&lt;sup&gt;14&lt;/sup&gt;</td>
<td>LA-EP2006 (pegfilgrastim, US) Chemotherapy induced neutropenia and others (same as originator)</td>
</tr>
</tbody>
</table>

1. Chronic myeloid leukemia
2. Non small cell lung cancer
3. Chronic spontaneous urticaria / chronic idiopathic urticaria
4. Neuroendocrine tumor
5. Breast cancer
6. Neuovascular age-related macular degeneration
7. Secondary prevention of cardiovascular events
8. Indolent Non-Hodgkin’s lymphoma
9. Non-radiographic axial spondyloarthritis
10. Psoriatic arthritis head-to-head study versus adalimumab
11. Akylosing spondylitis head-to-head study versus adalimumab
12. Diffuse large B-cell lymphoma
13. Preserved ejection fraction
14. Graft-versus-host disease
15. Multi-drug resistant
16. Retinopathy of prematurity
17. Severe aplastic anemia
18. Acute myeloid leukemia
19. Acute lymphoblastic leukemia
20. Secondary Progressive Multiple Sclerosis
21. Long-acting release
22. Chronic Lymphocytic Leukemia
23. IV formulation Type 1 SMA
24. 1st line colorectal cancer / 1st line renal cell carcinoma
25. IV formulation SMA Type 2/3

Combination abbreviations:
- ful = fulvestrant
- tux = timtuxetan
- tam = tamoxifen
- gos = goserelin
- tam = tamoxifen
- lu = letrozole
- nsai = non-steroidal aromatase inhibitor
- mek = Mekinist
- her = HER2
- mok = Mekinist® (trametinib)
- adv = adometastasal
- pk = Paclitaxel
- b = bhat
- h2h = head study versus
- spms = multiple sclerosis
- rmp = retinopathy of prematurity
- nAMD = neovascular age-related macular degeneration
- sx = spontaneous
- r = resistant
- nsai = non-steroidal aromatase inhibitor
- sba = spondyloarthritis
- st = standard
- gp = gosfilgrastim
- CSU = Csuloglycin
- PEF = pediatric failure
- LV = Lucentis
- BCL = B-cell lymphoma

*In collaboration with Amgen; companies to co-commercialize in the US, Novartis to have AMS 334 exclusive rights in rest of world excluding Japan.

*Approved in US, submitted in EU.
<table>
<thead>
<tr>
<th>Timing</th>
<th>Q&amp;A</th>
<th>Session</th>
<th>Presenters</th>
</tr>
</thead>
<tbody>
<tr>
<td>12:00 – 13:00</td>
<td></td>
<td>Registration / light lunch</td>
<td></td>
</tr>
<tr>
<td>13:00</td>
<td></td>
<td>Opening</td>
<td>Samir Shah</td>
</tr>
<tr>
<td>13:00 – 13:20</td>
<td>5 min</td>
<td>Pipeline, platforms</td>
<td>John Tsai</td>
</tr>
<tr>
<td>13:20 – 14:20</td>
<td>30 min</td>
<td>AveXis AVXS-101</td>
<td>Dave Lennon, Brian Kaspar</td>
</tr>
<tr>
<td>14:20 – 15:15</td>
<td>30 min</td>
<td>Oncology</td>
<td>Liz Barrett, Samit Hirawat</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Radioligand therapies, ACZ885 in NSCLC, SEG101, BYL719</td>
<td></td>
</tr>
<tr>
<td>15:15 – 15:45</td>
<td></td>
<td>Break</td>
<td></td>
</tr>
<tr>
<td>15:45 – 16:45</td>
<td>30 min</td>
<td>Upcoming launches (late-stage pipeline) QAW039, RTH258, BAF312, OMB157</td>
<td>John Tsai, Danny Bar Zohar, Paul Hudson</td>
</tr>
<tr>
<td>16:45 – 17:15</td>
<td>10 min</td>
<td>Near term value drivers Cosentyx®, Entresto®, Gilenya®</td>
<td>Paul Hudson, John Tsai</td>
</tr>
<tr>
<td>17:15 – 17:30</td>
<td>15 min</td>
<td>Q&amp;A session</td>
<td>Vas Narasimhan, Harry Kirsch, John Tsai, Paul Hudson, Liz Barrett</td>
</tr>
<tr>
<td>17:30</td>
<td></td>
<td>Cocktail</td>
<td>All</td>
</tr>
</tbody>
</table>
Key takeaways

1. **AVXS-101 foundational treatment for SMA: rapid, transformational and durable benefit in SMA Type 1**
   - US, EU, Japan regulatory approvals expected 1H 2019
   - Manufacturing capacity in place to deliver in launch markets
   - Partnering flexibly to introduce AVXS-101

2. **Full clinical program for AVXS-101 underway in all other SMA subtypes**
   - Pre-symptomatic and intrathecal study enrolling rapidly
   - Next major clinical readouts expected at AAN 2019

3. **Reproducible AAV gene therapy platform**
   - Potential to deliver multiple breakthrough treatments in CNS diseases
   - Up to 4 new AAV9 programs entering clinic in 2019
AveXis, a leading gene therapy company

- Novartis company headquartered in Bannockburn, Illinois
- Gene therapy manufacturing sites in Libertyville, IL and Raleigh, NC
- 500+ employees

**Gene therapy experts**

**AAV9 platform**

- Platform based on AAV9 technology, attractive vehicle for CNS diseases
- Emerging pipeline of AAV9-based assets, including Rett syndrome and genetic ALS entering clinic in 2019
AVXS-101 is a one-time treatment to restore production of SMN protein

Proprietary gene replacement therapy product candidate for the treatment of spinal muscular atrophy (SMA)

One-time treatment to restore production of SMN protein and to prevent further motor neuron death, thereby increasing motor function and enhancing survival

AVXS-101 has delivered rapid improvement in motor milestone achievements, dramatic survival benefit and a durable response, and favorable safety profile

Regulatory submissions achieved in the US, Europe and Japan for SMA Type 1
SMA is a devastating genetic neuromuscular disease

SMA is the #1 cause of genetic death in infants, affecting 1 in 10,000 live births

<table>
<thead>
<tr>
<th></th>
<th>TYPE 1</th>
<th>TYPE 2</th>
<th>TYPE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMN copy #</td>
<td>2 copies of SMN2</td>
<td>3-4 copies of SMN2</td>
<td>3-4 copies of SMN2</td>
</tr>
<tr>
<td>Age of onset</td>
<td>&lt;6 months</td>
<td>6-18 months</td>
<td>Early childhood to early adulthood (juvenile)</td>
</tr>
<tr>
<td>Incidence split</td>
<td>60%</td>
<td>30%</td>
<td>10%</td>
</tr>
<tr>
<td>Prevalence split (population)</td>
<td>14% (~3,300)</td>
<td>51% (~12,000)</td>
<td>35% (~8,200)</td>
</tr>
<tr>
<td>Survival</td>
<td>&lt;10% event-free by age 2</td>
<td>68% alive at age 25</td>
<td>Normal</td>
</tr>
</tbody>
</table>

1. Spinal Muscular Atrophy: Introduction to SMA families: SMA Foundation. 2. Estimate US, Japan, EU15, Australia, Canada, Turkey. 3. Event = Death or >= 16 hr/day ventilation continuously for >=2 weeks, in the absence of acute reversible illness.
## SMA patient opportunity in key geographies

<table>
<thead>
<tr>
<th>Region</th>
<th>Yearly incidence</th>
<th>Prevalent population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Type 1</td>
<td>Type 2</td>
</tr>
<tr>
<td>US</td>
<td>270-300</td>
<td>135-150</td>
</tr>
<tr>
<td>Europe</td>
<td>330-360</td>
<td>165-180</td>
</tr>
<tr>
<td>Japan</td>
<td>24-30</td>
<td>12-15</td>
</tr>
</tbody>
</table>

AXVS-101 gene therapy replaces defective *SMN1* gene producing normal (or greater) levels of SMN protein

<table>
<thead>
<tr>
<th>Normal individual</th>
<th>Individual with SMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMN genes → SMN protein</td>
<td>SMN genes → SMN protein</td>
</tr>
<tr>
<td>SMN1 Primary</td>
<td>SMN1 Primary</td>
</tr>
<tr>
<td>SMN2 Back up</td>
<td>SMN2 Back up</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SMA treated with splicing modulators</th>
<th>SMA treated with AVXS-101</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMN genes → SMN protein</td>
<td>SMN genes → SMN protein</td>
</tr>
<tr>
<td>SMN1 Primary</td>
<td>SMN1 Primary</td>
</tr>
<tr>
<td>SMN2 Back up</td>
<td>SMN2 Back up</td>
</tr>
</tbody>
</table>

- Functional SMN Protein
- Non-functional SMN Protein
## AAV9 is an ideal vector for gene transfer in CNS disease

<table>
<thead>
<tr>
<th>Transduction</th>
<th>Can be engineered for selective cell targeting and optimized transduction&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety</td>
<td>Non-pathogenic; designed to not integrate the transgene into the host genome&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Less immunogenic than other viruses</td>
</tr>
<tr>
<td></td>
<td>Low exposure in children (In our studies of SMA Type 1, only 1/41&lt;sup&gt;3&lt;/sup&gt; patients were excluded due to high AAV9 antibody titers)</td>
</tr>
<tr>
<td>Tropism</td>
<td>AAV serotypes display broad tropisms across the serotypes identified&lt;sup&gt;4,5&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>AAV9 crosses blood-brain barrier with high tropism for neuronal cells</td>
</tr>
<tr>
<td>Versatility</td>
<td>AAVs can be engineered for specific functionality in gene therapy applications&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**AVXS-101 designed to start producing SMN RNA and protein immediately & continuously**

---

**Continuous promoter**

Enhancer and promoter activates the transgene to allow for continuous and sustained SMN protein expression

---

**Human SMN transgene**

Full copy of a stable, functioning human *SMN* gene that is introduced into the cell’s nucleus

---

**Self-complementary AAV inverted terminal repeats (scAAV ITR)**

The scAAV ITR increases the speed at which the double-stranded transgene is transcribed and the resulting protein is produced

---

ITR, inverted terminal repeat; SV simian virus; Poly A, polyadenylation; scAAV, self-complementary AAV. Figure redrawn from Powel SK, et al. *Discov Med.* 2015;19:49–57.
AVXS-101 replaces *SMN1* gene with a working copy, promoting survival and proper function of motor neurons

- In mice models, AAV9 led to robust expression in cells throughout the brain and spinal cord, targeting >90% of spinal motor neurons.
- In non-human primates, intravenous AAV9 leads to robust, sustained transgene expression in 90% of motor neurons.
Intravenous AVXS-101 demonstrated rapid motor function improvements and survival in SMA mice

Mouse model video – left intentionally blank
One-time intrathecal (IT) gene therapy allows CNS-targeted, safe dosing in pediatric and adult patients

AVXS-101 Type 2 / 3 pediatric and adult, and older Type 1 studies will be based on IT formulation

1. One-time IT delivery
2. High transduction efficiency to motor neurons
3. Lower total viral load vs. one-time IV
4. Low viral exposure in periphery
Intrathecal AVXS-101 demonstrates remarkable transduction efficiency and durability in primates

Single cerebrospinal fluid (CSF) injection in non-human primates targets 55% to 80% of cervical, thoracic and lumbar spinal cord motor neurons
Intrathecal AVXS-101 demonstrated rapid motor function improvements and survival in large animal model of SMA

control

untreated

pre-symptomatic

symptomatic

video – left intentionally blank

video – left intentionally blank
AveXis developed cutting-edge manufacturing process to deliver AVXS-101

Robust, commercially scalable process
- Redesigned the Phase 1, institution-grade manufacturing process into commercial process
- Developed appropriate assays, process validation and reproducibility
- Demonstrated analytical comparability to FDA

In-house expertise
- Early development of best in breed adherent cell manufacturing process
- In-house analytical capabilities to fully own process and define product

Launch ready
- Currently building commercial inventory
- Fully capable of delivering sufficient IV doses for launch markets (US, EU, Japan)
- Tripling capacity with Durham, North Carolina site (planned to be operational by 2020)
AVXS-101 START trial and follow-up generating robust efficacy, safety and durability data

Cohort 1 (n=3)
Minimally-effective dose
Enrolled May – Sep 2014

Cohort 2 (n=12)
Proposed therapeutic dose
Enrolled Dec 2014 – Dec 2015

2-year safety follow-up

Study conclusion

15-year long-term follow-up

- Oldest patient >4 years old; >3.5 years of data
- 13 patients enrolled in LTFU study
  - 10/12 Cohort 2, 3/3 Cohort 1
  - 7/10 from Cohort 2 on AVXS-101 alone

LTFU – Long-term follow up

NEJM publication
AVXS-101 delivered rapid onset of effect, demonstrated by CHOP-INTEND, with most approaching max score
**AVXS-101 provides rapid and sustained efficacy regardless of severity at baseline**

<table>
<thead>
<tr>
<th>START(^1)</th>
<th>ENDEAR(^2)</th>
<th>FIREFISH(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AVXS</strong></td>
<td><strong>BIIB/IONIS</strong></td>
<td><strong>Roche/PTCT</strong></td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>One-time, IV dose</td>
<td>4 loading IT doses; Every 4 months maintenance</td>
</tr>
<tr>
<td><strong>Age (Months) at First Dose</strong></td>
<td>3.1</td>
<td>5.4</td>
</tr>
<tr>
<td><strong>Age (Months) at Last Assessment</strong></td>
<td>27.8</td>
<td>19.4</td>
</tr>
<tr>
<td><strong>Ability to Swallow at Baseline</strong></td>
<td>4/12 (33%)(^7)</td>
<td>41/80 (51%)(^5)</td>
</tr>
<tr>
<td><strong>Baseline CHOP-INTEND</strong></td>
<td>28.2</td>
<td>26.6</td>
</tr>
</tbody>
</table>

**Results**

<table>
<thead>
<tr>
<th>CHOP-INTEND Mean Increase</th>
<th>22.5 (n=12 @ 8 months)</th>
<th>10.5 (n=25 @ 10 months(^6))</th>
<th>16(^*) (n=14 @ 8 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOP-INTEND ≥4 point improvement</td>
<td>92% @ 1 month(^4)</td>
<td>71% @ 14 months</td>
<td>93% @ 8 months</td>
</tr>
</tbody>
</table>

3. Presented at the 23rd International Annual Congress of the World Muscle Society, Mendoza, Argentina, October 2–6, 2018  
4. Data on file  
5. swallowing or feeding difficulties  
7. defined as the ability to swallow thin liquids; *median; Where days were reported, they were converted to months by assuming 30 days per month; where weeks were reported, they were converted to months assuming 4 weeks per month.
**AVXS-101 demonstrated transformational milestone efficacy that continued in long term follow-up**

Cutoff: September 27, 2018

<table>
<thead>
<tr>
<th>Patient</th>
<th>Baseline CHOP-INTEND</th>
<th>Age at dosing</th>
<th>Swallowing at baseline</th>
<th>Sitting &gt;30 seconds$^1$</th>
<th>Standing with assistance$^1$</th>
<th>Eating by mouth$^2$</th>
<th>Nusinersen in LTFU$^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>E.4</td>
<td>29</td>
<td>6 months</td>
<td>YES</td>
<td></td>
<td></td>
<td></td>
<td>NO</td>
</tr>
<tr>
<td>E.5</td>
<td>29</td>
<td>4 months</td>
<td>YES</td>
<td></td>
<td></td>
<td></td>
<td>YES</td>
</tr>
<tr>
<td>E.6</td>
<td>47</td>
<td>2 months</td>
<td>YES</td>
<td></td>
<td></td>
<td></td>
<td>NO</td>
</tr>
<tr>
<td>E.7</td>
<td>25</td>
<td>4 months</td>
<td>NO</td>
<td></td>
<td></td>
<td></td>
<td>YES</td>
</tr>
<tr>
<td>E.8</td>
<td>12</td>
<td>8 months</td>
<td>NO</td>
<td></td>
<td></td>
<td></td>
<td>Not enrolled in LTFU</td>
</tr>
<tr>
<td>E.9</td>
<td>34</td>
<td>5 months</td>
<td>NO</td>
<td></td>
<td></td>
<td></td>
<td>Not enrolled in LTFU</td>
</tr>
<tr>
<td>E.10</td>
<td>50</td>
<td>1 month</td>
<td>YES</td>
<td></td>
<td></td>
<td></td>
<td>NO</td>
</tr>
<tr>
<td>E.11</td>
<td>16</td>
<td>2 months</td>
<td>NO</td>
<td></td>
<td></td>
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<td>NO</td>
</tr>
<tr>
<td>E.12</td>
<td>35</td>
<td>3 months</td>
<td>NO</td>
<td></td>
<td></td>
<td></td>
<td>NO</td>
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<tr>
<td>E.13</td>
<td>14</td>
<td>1 month</td>
<td>NO</td>
<td></td>
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<td>YES</td>
</tr>
<tr>
<td>E.14</td>
<td>30</td>
<td>4 months</td>
<td>NO</td>
<td></td>
<td></td>
<td></td>
<td>NO</td>
</tr>
<tr>
<td>E.15</td>
<td>17</td>
<td>2 months</td>
<td>NO</td>
<td></td>
<td></td>
<td></td>
<td>NO</td>
</tr>
</tbody>
</table>

1. Presented at the American Academy of Neurology (AAN) Annual Meeting, April 21-27, 2018, Los Angeles, California. 2. As of September 27, 2018 data cut; N/A, patient not enrolled in LTFU; mean age post gene replacement therapy in LTFU is 39 months

New milestone achieved in LTFU
Simultaneous regulatory license applications show significant progress for AVXS-101 in SMA Type 1

<table>
<thead>
<tr>
<th>Country</th>
<th>Status</th>
<th>Approval Timeline</th>
<th>Designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>BLA submitted to FDA at the end of Q3</td>
<td>Potential approval in 1H 2019 (6 months from file acceptance)</td>
<td>Breakthrough Therapy designation</td>
</tr>
<tr>
<td></td>
<td>MAA accepted</td>
<td>Potential approval in mid-2019 (7 months from file acceptance)</td>
<td>PRIME designation</td>
</tr>
<tr>
<td>Japan</td>
<td>JNDA submitted</td>
<td>Potential approval in 1H 2019</td>
<td>Sakigake designation</td>
</tr>
</tbody>
</table>

New update since Q3 earnings
86 patients dosed to date in broad clinical trial program covering all types of SMA

<table>
<thead>
<tr>
<th>Delivery</th>
<th>SMA Type</th>
<th>2014-2017</th>
<th>Q1 2018</th>
<th>Q2 2018</th>
<th>Q3 2018</th>
<th>Q4 2018</th>
<th>Q1 2019</th>
<th>Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous</td>
<td>Pre-symptomatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(IV) Type 1</td>
<td>Type 1,2,3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>START</strong></td>
<td>15 patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>STR1VÆ</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>STR1VÆ-EU</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>STR1VÆ-AP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intrathecal</td>
<td>Type 2</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>(IT) Type 1,2,3</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>STRONG</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td><strong>REACH</strong></td>
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<td></td>
<td></td>
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</tr>
</tbody>
</table>

Final design of REACH to be informed by STRONG

Pending

<table>
<thead>
<tr>
<th>START Phase 3</th>
<th>9 / 44 patients enrolled – data anticipated at AAN 2019</th>
<th>2020-2023</th>
</tr>
</thead>
<tbody>
<tr>
<td>STR1VÆ Phase 3</td>
<td>22 / 22 patients, fully enrolled – data anticipated at AAN 2019</td>
<td>2020</td>
</tr>
<tr>
<td>STR1VÆ-EU Phase 3</td>
<td>11 / 30 patients enrolled</td>
<td>2020</td>
</tr>
<tr>
<td>STR1VÆ-AP Planned start</td>
<td>Will enroll 6 patients</td>
<td>TBC</td>
</tr>
</tbody>
</table>

22 / 22 patients, fully enrolled – data anticipated at AAN 2019

29 / 51 patients; fully-enrolled in mid-dose cohort (26 / 26) – data anticipated by AAN 2019

86 patients dosed to date in broad clinical trial program covering all types of SMA

Novartis R&D and investor update | November 5, 2018
SMA Type 2 STRONG safety steps cleared and study mid-dose expansion cohort enrolled

Low-Dose Cohort
- 3 patients <24 months

Mid-Dose Cohort
- 3 patients <60 months
- 23 additional patients in expansion
- Total of 26 (13 <60 months and 13 <24 months)

High-Dose Cohort
- 3 patients <60 months
- 21 patients in expansion
- Total of 24 (12 >60 months and <24 months, 12 patients ≥24 and <60 months)

Initiated 1/18

Initiated 4/18

Expansions:
- Initiated 4/18
- Last patient enrolled 10/18
- Planned start 12/18

1 patient dosed / month

12 MONTHS
Branaplam (LMI070), an additional approach to the treatment of SMA

Phase 1 data presented at WMS demonstrate proof-of-concept

- Observed effects on motor skills support continued study of branaplam
- No clinical signs of neurotoxicity and appears to be well-tolerated
- The available data suggest a positive benefit vs. risk balance for the treatment of SMA Type 1

While gene therapy would be foundational in SMA, splice modulators may still have a role for the limited number of patients who do not qualify for gene therapy
AVXS-101 avoids burdens of chronic therapy

- One-time treatment
- One-hour infusion
- Out-patient
- Reduced anxiety
- Reduced caregiver burden

Safety and efficacy of AVXS-101 have not yet been evaluated by regulatory authorities.
Considerations in introducing a one-time, potentially curative therapy to healthcare system

1. Chronic vs. one-time treatment
2. Budget, cost of therapy over time
3. Payer fragmentation
4. Outcomes and duration
5. Payment models

“How should value-based prices for gene therapies reflect uncertainty regarding inclusion of additional elements of value that may be important for potential cures, but which are not part of standard cost-effectiveness methods?”

STEVE PEARSON
PRESIDENT, ICER

Office of Health Economics (OHE), Lunchtime Seminar, 10/22/18
“Time Is Neurons” – proposed solutions (under discussion)

**Policy Support**
- Partner with governments, hospitals, doctors and payers to support rapid diagnosis and treatment
- Support newborn screening implementation and pilot programs in the US and EU

**Program Support**
- Programs\(^1\) to encourage insurers to:
  - Facilitate SMA screening in newborns
  - Provide coverage for gene replacement therapy
  - Accelerate claims review mechanisms
  - To be available at launch in major markets as appropriate

**Patient Support**\(^1\)
- Program to cover out-of-pocket and travel costs for eligible patients
- No-cost patient assistance program for eligible U.S. patients experiencing financial hardship who have limited or no prescription drug coverage

1. Programs are not yet finalized
Value and pricing in life-long rare disease treatment

10-year drug cost vs. incremental QALY gained

<table>
<thead>
<tr>
<th>Disease</th>
<th>Prevalence in US</th>
</tr>
</thead>
<tbody>
<tr>
<td>GD Type 1</td>
<td>5,400¹</td>
</tr>
<tr>
<td>Fabry</td>
<td>3,800²</td>
</tr>
<tr>
<td>Hypophosphatasia</td>
<td>3,257³</td>
</tr>
<tr>
<td>Amyloidosis (hATTR)</td>
<td>3,250⁴</td>
</tr>
<tr>
<td>SMA Type I</td>
<td>1,260-1,400</td>
</tr>
<tr>
<td>MPS IV</td>
<td>1,086 to 1,629⁵</td>
</tr>
<tr>
<td>Hemophilia A Inhibitor with Inhibitors</td>
<td>961⁶</td>
</tr>
<tr>
<td>AHUS</td>
<td>900⁷</td>
</tr>
</tbody>
</table>

Disease Prevalence in US

<table>
<thead>
<tr>
<th>GD Type 1</th>
<th>Fabry</th>
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<th>Hemophilia A Inhibitor with Inhibitors</th>
<th>AHUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>5,400¹</td>
<td>3,800²</td>
<td>3,257³</td>
<td>3,250⁴</td>
<td>1,260-1,400</td>
<td>1,086 to 1,629⁵</td>
<td>961⁶</td>
<td>900⁷</td>
</tr>
</tbody>
</table>

AveXis established gene therapy platform reproducible for disease beyond SMA

<table>
<thead>
<tr>
<th>FDA guidance on gene therapy development</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>AveXis Gene Therapy Platform</th>
</tr>
</thead>
<tbody>
<tr>
<td>Establish well-controlled manufacturing process and suitable analytical assays early to ensure quality</td>
</tr>
<tr>
<td>✓ Validated manufacturing process</td>
</tr>
<tr>
<td>✓ Established AAV analytical methods</td>
</tr>
<tr>
<td>Study population should use existing data / natural history data to determine potential risks, benefits</td>
</tr>
<tr>
<td>✓ Neuromuscular and rare disease expertise</td>
</tr>
<tr>
<td>✓ Natural history study experience</td>
</tr>
<tr>
<td>Collect as much data as possible on every patient, and plan for long-term follow-up from outset</td>
</tr>
<tr>
<td>✓ Established protocols and experience to meet FDA expectations</td>
</tr>
<tr>
<td>✓ Over 90 patients treated in first program</td>
</tr>
<tr>
<td>Initiate product development discussions with the agency early</td>
</tr>
<tr>
<td>✓ Experience in securing appropriate designations to enable dialogue (e.g. Breakthrough Therapy)</td>
</tr>
</tbody>
</table>
## Novartis pipeline building and accelerating since AveXis acquisition

<table>
<thead>
<tr>
<th>Selected assets</th>
<th>Indication</th>
<th>Stage</th>
<th>Next milestone</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVXS-101 (AAV9)</td>
<td>SMA</td>
<td>Filed</td>
<td>Regulatory approval(s) 1H19</td>
</tr>
<tr>
<td>CGF166 (Ad5)(^1)</td>
<td>Hearing loss</td>
<td>Phase 1</td>
<td>PoC readout expected 2021</td>
</tr>
<tr>
<td>CPK850 (AAV8)(^1)</td>
<td>Retinitis pigmentosa</td>
<td>Phase 1</td>
<td>PoC readout expected 2020</td>
</tr>
<tr>
<td>AVXS-201 RTT (AAV9)</td>
<td>Rett Syndrome</td>
<td>Preclinical</td>
<td>IND 1Q19</td>
</tr>
<tr>
<td>AVXS-301 SOD1 (AAV9)</td>
<td>Inherited ALS-SOD1</td>
<td>Preclinical</td>
<td>IND 2Q19</td>
</tr>
<tr>
<td>AVXS-401</td>
<td>Undisclosed</td>
<td>Preclinical</td>
<td>IND 2H19</td>
</tr>
<tr>
<td>AVXS-501</td>
<td>Undisclosed</td>
<td>Preclinical</td>
<td>IND 4Q19 / 1Q20</td>
</tr>
</tbody>
</table>

POC – proof-of-concept  
1. Novartis Institute for Biomedical Research (NIBR) projects
# Agenda

<table>
<thead>
<tr>
<th>Timing</th>
<th>Q&amp;A</th>
<th>Session</th>
<th>Presenters</th>
</tr>
</thead>
<tbody>
<tr>
<td>12:00 – 13:00</td>
<td></td>
<td>Registration / light lunch</td>
<td></td>
</tr>
<tr>
<td>13:00</td>
<td></td>
<td>Opening</td>
<td>Samir Shah</td>
</tr>
<tr>
<td>13:00 – 13:20</td>
<td>5 min</td>
<td>Pipeline, platforms</td>
<td>John Tsai</td>
</tr>
<tr>
<td>13:20 – 14:20</td>
<td>30 min</td>
<td>AveXis AVXS-101</td>
<td>Dave Lennon, Brian Kaspar</td>
</tr>
<tr>
<td>14:20 – 15:15</td>
<td>30 min</td>
<td><strong>Oncology</strong>&lt;br&gt;Radioligand therapies, ACZ885 in NSCLC, SEG101, BYL719</td>
<td><strong>Liz Barrett, Samit Hirawat</strong></td>
</tr>
<tr>
<td>15:15 – 15:45</td>
<td></td>
<td>Break</td>
<td></td>
</tr>
<tr>
<td>15:45 – 16:45</td>
<td>30 min</td>
<td>Upcoming launches (late-stage pipeline)&lt;br&gt;QAW039, RTH258, BAF312, OMB157</td>
<td>John Tsai, Danny Bar Zohar, Paul Hudson</td>
</tr>
<tr>
<td>16:45 – 17:15</td>
<td>10 min</td>
<td>Near term value drivers&lt;br&gt;Cosentyx®, Entresto®, Gilenya®</td>
<td>Paul Hudson, John Tsai</td>
</tr>
<tr>
<td>17:15 – 17:30</td>
<td>15 min</td>
<td>Q&amp;A session</td>
<td>Vas Narasimhan, Harry Kirsch, John Tsai, Paul Hudson, Liz Barrett</td>
</tr>
<tr>
<td>17:30</td>
<td></td>
<td>Cocktail</td>
<td>All</td>
</tr>
</tbody>
</table>
Focused on transformational platforms with differentiated and blockbuster potential medicines in each

<table>
<thead>
<tr>
<th>CAR-T</th>
<th>Radioligand therapies</th>
<th>Immunotherapies</th>
<th>Targeted therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAR-T</td>
<td><strong>Kymriah</strong>® in</td>
<td><strong>ACZ885</strong> in</td>
<td><strong>ABL001</strong> in CML (3rd line and 1st line)</td>
</tr>
<tr>
<td></td>
<td>– CLL</td>
<td>– adjuvant NSCLC</td>
<td><strong>BYL719</strong> in PIK3CA mutated advanced HR+/HER2-breast cancer</td>
</tr>
<tr>
<td></td>
<td>– r/r DLBCL in 1st relapse</td>
<td>– 1st line NSCLC</td>
<td>HDM201 in Acute myeloid leukemia</td>
</tr>
<tr>
<td></td>
<td>– r/r follicular lymphoma</td>
<td>– 2nd line NSCLC</td>
<td>INC280 in NSCLC, single agent and combination</td>
</tr>
<tr>
<td></td>
<td>– combination with pembrolizumab in r/r DLBCL</td>
<td><strong>PDR001</strong>, metastatic BRAF V600+ melanoma</td>
<td><strong>Jakavi</strong>® in Chronic and acute GvHD</td>
</tr>
<tr>
<td></td>
<td>– Adult ALL</td>
<td><strong>PDR001</strong>, multiple combinations in Metastatic melanoma</td>
<td><strong>Kisqali</strong>® in HR+ HER2- BC (adjuvant)</td>
</tr>
<tr>
<td></td>
<td>Agreement to acquire <strong>Endocyte</strong>; first-to-market potential in lead product1</td>
<td><strong>VPM087</strong> in 1st line CRC / 1st line RCC</td>
<td><strong>LCI699</strong> in Cushing’s disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Rydapt®</strong> in AML, FLT3 wild type</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>SEG101</strong> in Sickle cell disease</td>
</tr>
</tbody>
</table>

Projects included are those with planned filings in US and/or EU

---

1. The acquisition of **Endocyte** is subject to customary closing conditions, including receipt of regulatory approvals and **Endocyte** stockholders approval. Until closing, **Endocyte** will continue to operate as a separate and independent company.

---

Will be discussed in this presentation
Novartis has one of the most comprehensive CAR-T development programs across multiple indications

- Optimizing manufacturing; advancing multiple indications beyond pediatric & young adult r/r ALL and r/r DLBCL
- Can be infused as an outpatient therapy and 4-1BB construct provides for a better safety profile

<table>
<thead>
<tr>
<th>CAR-T Type</th>
<th>Cancer indication</th>
<th>Phase 1</th>
<th>Phase 2/pivotal</th>
<th>Phase 3</th>
<th>Submitted</th>
<th>Approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD19 CAR-T</td>
<td>Pediatric &amp; young adult r/r ALL&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>US, EU</td>
</tr>
<tr>
<td>CD19 CAR-T</td>
<td>r/r DLBCL&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>US, EU</td>
</tr>
<tr>
<td>CD19 CAR-T</td>
<td>DLBCL in 1st relapse&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td>Starting 2019</td>
<td></td>
</tr>
<tr>
<td>CD19 CAR-T</td>
<td>r/r FL&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td>Starting 2018</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD19 CAR-T</td>
<td>r/r DLBCL&lt;sup&gt;2&lt;/sup&gt; in combination with pembrolizumab</td>
<td>Started 2018</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD19 CAR-T</td>
<td>Adult r/r ALL</td>
<td></td>
<td></td>
<td></td>
<td>Starting 2019</td>
<td></td>
</tr>
<tr>
<td>CD19 CAR-T</td>
<td>CLL&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td>Starting 2019</td>
<td></td>
</tr>
<tr>
<td>CAR-T-BCMA</td>
<td>r/r MM&lt;sup&gt;5&lt;/sup&gt; combination</td>
<td></td>
<td></td>
<td></td>
<td>Started 2018</td>
<td></td>
</tr>
</tbody>
</table>

Novartis is investing to build leading radioligand therapy platform for cancer

**177Lu Isotope**
Produced in nuclear reactors

**Isotope supply**  
**Production**  
**Hospital**

---

**Precursor Isotope**

**Target Isotope**

**Octreotide DOTA-TATE**
Aseptic vial filling

**Lutathera® labeling**

**Lutathera®**
Aseptic conditions  
On demand production

**Patient dose**
Standard dose of 7.4GBq/cycle  
Aseptic conditions

**Patient delivery**
Significant patient population for GEP-NET

<table>
<thead>
<tr>
<th>Category</th>
<th>Incidence (in thousands)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total incidence, GEP-NET</td>
<td>36</td>
<td>100%</td>
</tr>
<tr>
<td>Grade 1 &amp; 2</td>
<td>32</td>
<td>89%</td>
</tr>
<tr>
<td>Unresectable/progressive</td>
<td>27</td>
<td>85%</td>
</tr>
<tr>
<td>With SST receptors</td>
<td>26</td>
<td>96%</td>
</tr>
<tr>
<td>2nd Line</td>
<td>22</td>
<td>85%</td>
</tr>
<tr>
<td>3rd Line</td>
<td>15</td>
<td>70%</td>
</tr>
</tbody>
</table>

All data for US and EU5 in 2017
1. Datamonitor Market Spotlight report, Oct. 2018
**Overview of Lutathera® (lutetium Lu 177 dotatate)**

- Lutathera® belongs to an innovative drug category called **RadioLigand Therapy (RLT)**. RLT involves the systemic administration of a radiopharmaceutical to deliver cytotoxic radiation to a tumor.
- Received FDA approval for treatment of Gastroenteropancreatic Neuroendocrine Tumors in January 2018; first FDA approval for a Peptide Receptor Radionuclide Therapy.
- Lutetium Lu 177 dotatate is composed of a lutetium 177 radionuclide chelated to a peptide. Lutetium emits mostly high energy electrons (β-particles; half-life 6.6 days).
- The peptide is designed to target somatostatin receptors with high binding affinity.

---

1. USAN: lutetium Lu 177 dotatate / INN: lutetium (177Lu) oxo-olotretotide
Lutathera® demonstrated significant PFS improvement in patients with neuroendocrine tumor (NET)

Hazard ratio: 0.21
[0.13 – 0.32]
P = <0.0001

79% reduction in risk of disease progression or death

Approved in US and EU
Showing rapid uptake as best second line option after somatostatin analogues
>1,100 patients treated in US October 2018 YTD; 85+ centers prescribing
2 months after UK reimbursement, 18 centers prescribing

N = 229 (ITT)
LUTATHERA® arm: 27
Octreotide LAR 60 mg: 78
### AAA pipeline includes projects in indications beyond NET

<table>
<thead>
<tr>
<th>Product</th>
<th>Disease (target)</th>
<th>Preclinical</th>
<th>Ph1</th>
<th>Ph2</th>
<th>Ph3</th>
<th>Filing</th>
<th>Marketed</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lutetium Lu 177 dotatate*</td>
<td>Neuroendocrine tumors (SSTR2)</td>
<td>Therapeutic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Approved US / EU</strong>&lt;br&gt;<strong>Ongoing ISS for expanded indications/combinations</strong></td>
</tr>
<tr>
<td>Gallium Ga 68 dotatate/edotreotide</td>
<td>PET Diagnostic (US)&lt;br&gt;PET Diagnostic (EU)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Approved US / EU</strong>&lt;br&gt;<strong>Ongoing ISS for additional indications</strong></td>
</tr>
<tr>
<td>177Lu PSMA-R2</td>
<td>Prostate cancer (PSMA)</td>
<td>Therapeutic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Ph1/2 study initiated 2Q-2018</strong></td>
</tr>
<tr>
<td>68Ga PSMA-R2</td>
<td>PET Diagnostic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Ph1/2 study initiated 2Q-2018</strong></td>
</tr>
<tr>
<td>18F CTT1057</td>
<td>PET Diagnostic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Ph1 study completed</strong></td>
</tr>
<tr>
<td>177Lu NeoBOMB1</td>
<td>Breast Cancer&lt;br&gt;Colorectal Cancer&lt;br&gt;Lung Cancer, others</td>
<td>Therapeutic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Ph1/2 study planned 1H-2019</strong></td>
</tr>
<tr>
<td>68Ga NeoBOMB1</td>
<td>PET Diagnostic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Ph1 ISS in GIST completed&lt;br&gt;Ph2 study initiated 2Q-2018</strong></td>
</tr>
</tbody>
</table>

*USAN lutetium Lu 177 dotatate / INN: lutetium (177Lu) oxodotreotide.
Significant patient population for prostate cancer

Prostate Cancer\(^1\)
(in thousands)

- Incidence + newly recurrent, stage IV metastatic PC: 196 (100%)
- Castrate resistant (mCRPC): 88 (45%)
- PSMA+: 70 (80%)
  - 2\(^{nd}\) Line: 75 (107%)
  - 3\(^{rd}\) Line: 49 (65\(^2\))
  - 4\(^{th}\) Line: 25 (51\(^2\))

Note: Higher percentage of metastatic patients in later lines.

Initial 177Lu-PSMA-617 target patient pool\(^3\)

---

All data for US and EU in 2017
2. Percentage of patients in later lines of therapies was calculated based on the treatment rate of the previous line.
3. The acquisition of Endocyte is subject to customary closing conditions, including receipt of regulatory approvals and Endocyte stockholders approval. Until closing, Endocyte will continue to operate as a separate and independent company.
Endocyte uses small molecule ligand to direct radioactive atom to PSMA-expressing cancer cells

RLT that utilizes high affinity targeting ligand to direct potent radiotherapy to prostate cancer cells

$^{177}$Lu-PSMA-617 pairs PSMA targeting ligand (PSMA-617) to radioactive atom ($^{177}$Lutetium)

“Ligand” is a small molecule designed to bind to PSMA, a protein highly expressed on the cell surface of most prostate cancer cells

Once bound, the $^{177}$Lutetium atom releases an energetic beta particle that kills the cancer cell
Endocyte\textsuperscript{1} has strong Ph2 clinical data

Sustained response rates in Ph2 trial expansion\textsuperscript{2}

PSA response

\begin{align*}
\text{%} & \quad <30\% & \quad \geq 30\% & \quad \geq 50\% \\
13/50 & \quad (26\%) & \quad 37/50 & \quad (74\%) & \quad 31/50 & \quad (62\%)
\end{align*}

PSA PFS and OS correlate to PSA response and compare favorably to historical benchmarks\textsuperscript{2}

PSA PFS

50 patients

Overall Survival

First 30 patients

p-value comparing PSA <50% group to PSA ≥ 50% group;
Updated data cut-off since Lancet publication


1. The acquisition of Endocyte is subject to customary closing conditions, including receipt of regulatory approvals and Endocyte stockholders approval. Until closing, Endocyte will continue to operate as a separate and independent company.

Endocyte\(^1\) pivotal Ph3 trial design with FDA agreement to rPFS as alternative primary endpoint to OS\(^2\)

Patient inclusion
- mCRPC
- Bone and/or soft tissue disease
- PSMA-positive scan (~80%)
- ≥1 prior taxane
- ≥1 prior NAAD\(^4\)

\[177\text{Lu-PSMA-617} \]

- Best supportive care\(^3\)
- Choice of NAAD\(^3\) or not

\[\text{Best supportive care}\(^3\) \]

- Choice of NAAD\(^4\) or not

- 750 patients, enrollment initiated
- In September, FDA agreed to rPFS as an alternative primary endpoint to OS as sufficient for full approval\(^2\)
- Key secondary endpoints: ORR, time to symptomatic skeletal events

Source: Endocyte Investor Presentation October 2018. 1. The acquisition of Endocyte is subject to customary closing conditions, including receipt of regulatory approvals and Endocyte stockholders approval. Until closing, Endocyte will continue to operate as a separate and independent company. 2. Endocyte stated demonstrating benefit in rPFS (radiographic Progression Free Survival) versus control, with no detriment to OS, sufficient for full approval; regardless of the outcome of rPFS assessment, Endocyte intends to continue to follow patients in VISION trial to assess final OS alternative primary endpoint as per Endocyte press release on September 10, 2018. 3. Best supportive care – palliative; 4. NAAD – novel androgen axis drug (abiraterone or enzalutamide).
Radioligand therapies key takeaways

1. Lutathera® belongs to an innovative drug category called radioligand therapy and shows strong launch momentum with Q3 2018 sales of USD 56m

2. The AAA (radioligand therapy) pipeline has projects in development for indications beyond NET

3. Novartis has announced an agreement to acquire Endocyte, which would expand the company’s nuclear medicines platform

---

1. The acquisition of Endocyte is subject to customary closing conditions, including receipt of regulatory approvals and Endocyte stockholders approval. Until closing, Endocyte will continue to operate as a separate and independent company.
Canakinumab (ACZ885) targeting IL-1β innate immunity pathway may markedly impact cancer

- **IL-1β** is elevated in various cancers, including breast, lung, colon, and melanomas\(^1\), and has been associated with poor prognosis across cancers\(^1\)

- **CANTOS trial**’s exploratory analysis regarding relative risk reduction (RRR) in cancer mortality was encouraging
  - Incident cancers and cancer deaths was **prospective, blinded safety analysis** adjudicated by an independent Oncology monitoring committee as agreed with FDA in 2010
  - Dose dependent 51% RRR in total cancer mortality (\(p=0.0009\), 300mg); 77% RRR in lung cancer mortality (\(p=0.0002\), 300mg); 67% RRR in incident lung cancers (\(p=0.00008\), 300mg)
  - History of cancer was an exclusion criteria to study enrollment; baseline CT scans were not conducted, but subsequent sample analysis found presence of circulating tumor DNA in baseline samples of patients diagnosed with lung cancer
  - Published data on therapies with higher efficacy of treatment correlated with suppression of hsCRP provide rationale for exploring canakinumab

- Scientific rationale, encouraging findings from CANTOS trial, and established safety profile of Ilaris® supported **prospective Ph3 studies across Stage II – IV NSCLC, which are now ongoing**

- IL-1, interleukin-1; IL-1α, interleukin-1α; IL-1β, interleukin-1β; MDSC, myeloid-derived suppressor cell; NSCLC, non-small cell lung cancer; hsCRP, high-sensitivity C-reactive protein

CRP is associated with lung cancer risk, tumor size, and progression

- CRP is measured by high-sensitivity assay (hsCRP) techniques\(^1\)
- Elevated CRP is associated with a higher risk of developing lung cancer\(^2,3\)
- CRP is elevated in NSCLC, correlates with tumor size and stage, and points to poor outcome and prognosis\(^4,5\)

**A. Correlation coefficient between lung tumor size and serum CRP level showing a significant linear relationship (P<0.05)\(^2\)**

**B. Serum CRP levels in healthy controls vs localized and metastatic NSCLC\(^3\)**

---

Figure from the Egyptian Journal of Chest Diseases and Tuberculosis, Copyright 2014, https://doi.org/10.1016/j.ejcdt.2014.02.003. Aref H, et al., CRP evaluation in non-small cell lung cancer, licensed under CC BY 4.0.
Baseline CRP may predict survival following PD-1 therapy in lung cancer

Late stage NSCLC & SCLC patients (N=99) treated with nivolumab after first line platinum-doublet with median baseline CRP was 22 mg/L

Median OSI (Overall Survival after Immunotherapy) after nivolumab treatment for baseline CRP ≤ 50 mg/L was 9.3 months, vs 2.7 months for CRP > 50mg/L (P=0.014)

IASLC Nov. 2017 Abstract 4A. Naquash AR et al. Predictive Utility of CRP in Advanced Stage Lung Cancer Treated with Anti-PD-1 Therapy
Canakinumab: monoclonal antibody that targets IL-1β

Canakinumab is a human IgGκ monoclonal antibody with high affinity and specificity for IL-1β (dissociation equilibrium constant 35–40 pM)\(^1,2\)

IL, interleukin; IL-1RI, IL-1 type I receptor; IL1Ra, IL-1 receptor antagonist; IL-1RacP, IL-1R accessory protein.  

For presentation in response to an unsolicited request for medical information subject to local approval. Not for distribution
Reduced diagnosis of overt NSCLC and fatal lung cancer observed in canakinumab arms of CANTOS

Rate of lung cancer

Dose-dependent effect, 67% relative risk reduction (canakinumab 300mg)

<table>
<thead>
<tr>
<th>Dose</th>
<th>HR</th>
<th>(95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1.0</td>
<td>(ref)</td>
<td>(ref)</td>
</tr>
<tr>
<td>Canakinumab 50 mg</td>
<td>0.74</td>
<td>(0.47-1.37)</td>
<td>0.20</td>
</tr>
<tr>
<td>Canakinumab 150 mg</td>
<td>0.61</td>
<td>(0.39-0.97)</td>
<td>0.034</td>
</tr>
<tr>
<td>Canakinumab 300 mg</td>
<td>0.33</td>
<td>(0.18-0.59)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

p trend across groups<0.0001

Rate of lung cancer mortality

Dose-dependent effect, 77% relative risk reduction (canakinumab 300mg)

<table>
<thead>
<tr>
<th>Dose</th>
<th>HR</th>
<th>(95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1.0</td>
<td>(ref)</td>
<td>(ref)</td>
</tr>
<tr>
<td>Canakinumab 50 mg</td>
<td>0.67</td>
<td>(0.37-1.20)</td>
<td>0.18</td>
</tr>
<tr>
<td>Canakinumab 150 mg</td>
<td>0.64</td>
<td>(0.36-1.14)</td>
<td>0.33</td>
</tr>
<tr>
<td>Canakinumab 300 mg</td>
<td>0.23</td>
<td>(0.10-0.54)</td>
<td>&lt;0.0002</td>
</tr>
</tbody>
</table>

p trend across groups<0.0002

>70% baseline samples with detectable ctDNA with lung cancer driver mutations (p53, EGFR, etc.)

- In agreement with FDA in 2010, incident cancers were adjudicated by a blinded independent Oncology monitoring committee
- Data on incident cancers including cancer deaths were collected as serious adverse events and analyzed in a prospective fashion
- Statistical analysis of cancer incidence and cancer deaths was pre-planned
# Three Ph3 trials (CANOPY) to explore role of canakinumab in NSCLC

<table>
<thead>
<tr>
<th>Indication</th>
<th>Ph3 trial name and code</th>
<th>Patient population</th>
<th>Trial design</th>
<th>Planned filing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant NSCLC</td>
<td>CANOPY-A</td>
<td>High-Risk Stage II-III</td>
<td>Canakinumab vs. placebo (N=1500 with 1:1 randomization) after post-resection chemotherapy</td>
<td>2022</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; line NSCLC</td>
<td>CANOPY-1</td>
<td>Non-mutated, no prior treatment for metastatic disease or Stage III unresectable</td>
<td>Platinum doublet chemotherapy and pembrolizumab with or without canakinumab (N=600 with 1:1 randomization)</td>
<td>2021</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line NSCLC</td>
<td>CANOPY-2</td>
<td>Patients with no more than 2 prior lines of metastatic treatment</td>
<td>Docetaxel with or without canakinumab (N=226 with 1:1 randomization)</td>
<td>2021</td>
</tr>
</tbody>
</table>
Poor long-term outcomes in patients with early stage lung cancer

- 25-30% of patients are diagnosed early enough for surgical resection¹
- With surgical resection alone, recurrence rate is high (~60% at five years)²
- Modest reduction of risk of recurrence with cisplatin-based adjuvant chemotherapy³
- Significant unmet medical need remains for patients with resectable Stage II-III disease⁴
  - Improving current approaches to adjuvant SOC is needed
  - Novel approaches to neo-adjuvant therapy could additionally improve resectability and long term outcomes

Canakinumab: adjuvant NSCLC program (CANOPY-A)

Patient eligibility criteria
- High risk (Stages IIA-IIIA and IIIB with T>5cm, N2) & R0 resection
- All histologies
- Post SoC adjuvant cisplatin-based chemotherapy (and SoC RT, if applicable)

Start date
Ph3 trial started in March 2018.
Recruitment ongoing

Expected primary completion date
(i.e., data available date leading to filing)

Planned filing
H2-2021
H1-2022

Study endpoints
- Primary: RFS
- Secondary: OS

Opportunity
~25-30% of NSCLC eligible for treatment\(^1\)

Current standard of care is surgery followed by Chemotherapy +/- RT

Canakinumab: scientific rationale for combining canakinumab with anti-PD-1 therapy

- CRP is prognostic/predictive of anti-PD-1/PD-L1 activity in NSCLC; anti-PD-1 appears to be less efficacious in patients with chronic inflammation.
- Recent data has demonstrated that serum acute phase reactants and other chronic inflammatory proteins are associated with short survival with PD-1 blockade.
- Unpublished data demonstrate that CRP, Serum Amyloid A, and other acute phase reactants have profound inhibitory effects on T cell proliferation and function, alter T cell phenotype and suppress dendritic cell activation and function, thus contributing to a more immunosuppressive TME.
- Inhibiting IL1b is hypothesized to have a favorable effect on the tumor microenvironment thereby enhancing the efficacy of SOC chemo-immunotherapy.
ALK(-), EGFR(-) patients represent ~80% of metastatic NSCLC patients.

Various IO+/- chemo and targeted therapies available

Canakinumab combination with pembrolizumab could become standard of care

Study design

**Patient eligibility criteria**
- Confirmed Stage IIIB, IV NSCLC [no driver mutations]
- Squamous and Non-Squamous
- No prior therapy for metastatic disease

**Study endpoints**
- Primary: PFS & OS
- Secondary: ORR, DoR, DCR, TTR and Safety

**Study design**

<table>
<thead>
<tr>
<th>Safety run in</th>
<th>Randomization 1:1</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=27</td>
<td>N=600</td>
</tr>
</tbody>
</table>

**Canakinumab vs. placebo**
Backbone therapy
**INDUCTION**
Platinum doublet + pembrolizumab 4 cycles **MAINTENANCE**
Pembrolizumab +/- pemetrexed

**Timelines**

- **Start date**: Ph3 planned to start in December 2018
- **Expected primary completion date**: (i.e., data available date leading to filing)
  - H1-2021
- **Planned filing**: H2-2021

**Opportunity**

<table>
<thead>
<tr>
<th>PFS – progression free survival</th>
<th>OS – overall survival</th>
<th>ORR – overall response rate</th>
<th>DoR – duration of response</th>
<th>DCR – disease control rate</th>
<th>TTR – time to progression</th>
</tr>
</thead>
</table>

Canakinumab: high unmet medical need remains for unresectable or metastatic NSCLC

- ~70% of patients present with unresectable or metastatic disease\(^1\)
- Majority of the patients do not have a molecularly targetable driver mutation
- Outcomes of 1L treatment remain dismal; most patients fail treatment in less than a year and die within two years of diagnosis\(^2,3\)
- Docetaxel as single agent is established SOC with very modest efficacy
  - Progression free survival of ~3 months
  - Overall survival ~8 months

---

Canakinumab: 2nd line NSCLC (CANOPY-2)

**Study design**

**Patient eligibility criteria**
- Stage IIIB or IV NSCLC [no driver mutations]
- Previously treated with platinum therapy and PD(L)1-inhibitor
- Measurable disease

**Study endpoints**
- Primary: OS
- Secondary: PFS, ORR, DOR

**Timelines**

**Start date**
- Ph3 planned to start in December 2018

**Expected primary completion date**
- (i.e., data available date leading to filing)
- H1-2021

**Planned filing**
- H2-2021

**Opportunity**

Only current option post IO treatment is chemotherapy
Canakinumab key takeaways

1. There is a high unmet medical need and poor long-term outcomes for patients with NSCLC

2. CANTOS trial showed reduction in incidence of lung cancer and fatal lung cancer in canakinumab arm

3. Three Ph3 trials ongoing in adjuvant NSCLC, 1st line NSCLC, and 2nd line NSCLC for canakinumab to become an additional treatment option in these settings
Strong presence in hematology helps drive greater potential for crizanlizumab (SEG101)¹

<table>
<thead>
<tr>
<th>Chronic Myelogenous Leukemia</th>
<th>Acute Myeloid Leukemia</th>
<th>Acute Lymphocytic Leukemia Diffuse Large B-Cell Lymphoma</th>
<th>Myeloproliferative Neoplasms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tassigna (nilotinib)</td>
<td>gleevec (imatinib mesylate)</td>
<td>KYMRIAH™ (tisagenlecleucel) Suspension for IV infusion</td>
<td>JAKAVI (ruxolitinib)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immune Thrombocytopenia</th>
<th>Iron Overload</th>
<th>Sickle Cell Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROMACTA® (eltrombopag)</td>
<td>JADENU® (deferasirox)</td>
<td>Crizanlizumab (SEG101)¹</td>
</tr>
</tbody>
</table>

1. Planned filings in US and EU in H1 2019
Opportunity is significant for crizanlizumab by helping patients with SCD to have more VOC-free days

### Large SCD patient population with high unmet need
- ~100,000 patients in US\(^1\) and ~45,000 in Europe\(^2\)
- 3 out of 5 adult SCD patients have ≥2 VOC per year\(^2\)
- VOC is #1 cause of hospitalization in SCD; ~200,000 US emergency visits per year\(^3,4\)

### Crizanlizumab is highly differentiated
- 1\(^{st}\) drug to target multi-cell adhesion, a key driver of VOC
- Clinical efficacy is demonstrated with or without HU
- Monthly administration, which could facilitate compliance

### Population with some access and compliance challenges but expected to improve with new effective treatment
- ~40% of adults treated in specialty centers (>80% of children)
- Most covered by Medicaid / Medicare, but accessible with good value proposition
- Compliance rate on oral medications in SCD is ~50%

---

<table>
<thead>
<tr>
<th>VOC Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1 VOC / year</td>
<td>42%</td>
</tr>
<tr>
<td>2-4 VOC / year</td>
<td>33%</td>
</tr>
<tr>
<td>5+ VOC / year</td>
<td>25%</td>
</tr>
</tbody>
</table>

---

VOC=Vaso-occlusive crisis; SCD=Sickle Cell Disease, HU: hydroxyurea  
Multi-cell adhesion, mediated by p-selectin, is a key driver of VOCs

**Interactions and adhesion** of red blood cells, white blood cells, platelets and endothelial cells are critical to pathophysiology

- Increased adhesion is due to vascular damage that develops early in SCD patients, exacerbated by reduced erythrocyte deformability

This causes chronic vascular inflammation and **promotes vaso-occlusion**

**P-selectin**, a cell adhesion molecule on the surfaces of activated endothelial cells and platelets, plays a critical role in vaso-occlusion by mediating the tethering of blood cell and endothelial cell adhesions

Crizanlizumab, a p-selectin inhibitor, has shown to reduce frequency of VOCs in pivotal SUSTAIN trial

**Median annual rate of VOC**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Crizanlizumab 5 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>VOC rate</td>
<td>2.98</td>
<td>1.63</td>
</tr>
<tr>
<td>Reduction</td>
<td>-45.3%</td>
<td></td>
</tr>
</tbody>
</table>

Crizanlizumab 5 mg/kg showed statistically significant and **clinically meaningful reduction** of VOCs that led to a healthcare visit

**Potential disease-modifying therapy**

Planned US and EU filings in H1–2019
(Bridging study in healthy volunteers completed and PK/PD study completed enrollment necessary for submission)

---

Note: SUSTAIN trial was randomized, double-blinded, placebo-controlled  
1. VOC=Vaso-occlusive crisis that led to a healthcare visit; 2. HU=Hydroxyurea; 3. Stratified Wilcoxon Rank Sum test; 4. Hodges-Lehmann median difference (95% CI).
Crizanlizumab increased proportion of patients free from VOC and delayed these crises

Proportion of patients free from VOC for the study period¹

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Crizanlizumab 5 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.9%</td>
<td>35.8%</td>
</tr>
</tbody>
</table>

> 2x

p = 0.013

Time to first VOC¹

Median for crizanlizumab 5 mg/kg vs. placebo
4.07 vs 1.38 months

VOCs are associated with increased morbidity / mortality, can result in stroke, as well as organ damage or failure²

¹ VOC that led to healthcare visit; p= 0.001 (log rank p-value); HR (95%CI) = 0.50 (0.33, 0.74); Kutlar et al, Am J Hematol. 2018 Oct 8. doi: 10.1002/ajh.25308.
SUSTAIN study showed consistent results across subgroups

VOC leading to healthcare visit annual rates, by subgroup (standard median)

<table>
<thead>
<tr>
<th>Concomitant HU/HC</th>
<th>Number of crises in previous 12 months</th>
<th>Sickle cell disease genotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p² = 0.084</td>
<td>p² = 0.046</td>
</tr>
<tr>
<td></td>
<td>HL¹ = -1.01</td>
<td>HL¹ = -1.02</td>
</tr>
<tr>
<td></td>
<td>(-2.44, 0.00)</td>
<td>(-2.00, 0.00)</td>
</tr>
</tbody>
</table>

Placebo  Crizanlizumab 5mg/kg

- Yes
  - n=40
    - Crizanlizumab: 3.58
    - Placebo: 2.43
    - p² = 0.084
    - HL¹ = -1.01
    - (-2.44, 0.00)
  - n=25
    - Crizanlizumab: 2.00
    - Placebo: 1.00

- No
  - n=42
    - Crizanlizumab: 2.00
    - Placebo: 1.00
    - p² = 0.046
    - HL¹ = -1.02
    - (-2.00, 0.00)

- 2-4 crises
  - n=41
    - Crizanlizumab: 1.14
    - Placebo: 2.00
    - p² = 0.279
    - HL¹ = -0.05
    - (-1.56, 0.01)

- 5-10 crises
  - n=24
    - Crizanlizumab: 1.97
    - Placebo: 5.32
    - p² = 0.005
    - HL¹ = -2.74
    - (-5.00, -0.83)

- HbSS
  - n=47
    - Crizanlizumab: 3.01
    - Placebo: 1.97
    - p² = 0.005
    - HL¹ = -2.74
    - (-5.00, -0.83)

- Non HbSS
  - n=18
    - Crizanlizumab: 2.00
    - Placebo: 2.00
    - p² = 0.223
    - HL¹ = -1.01
    - (-2.01, 0.00)

1. Hodges-Lehmann median difference (95% CI).
Crizanlizumab: low incidence of adverse events

Overall incidence of adverse events

Any TEAE

<table>
<thead>
<tr>
<th>Any TEAE</th>
<th>Placebo</th>
<th>Crizanlizumab 2.5 mg/kg</th>
<th>Crizanlizumab 5 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>88.7%</td>
<td>87.5%</td>
<td>86.4%</td>
<td></td>
</tr>
</tbody>
</table>

Incidence of selected adverse events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo</th>
<th>Crizanlizumab 2.5 mg/kg</th>
<th>Crizanlizumab 5 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgia</td>
<td>8.1%</td>
<td>14.1%</td>
<td>18.2%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3.2%</td>
<td>7.8%</td>
<td>10.6%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3.2%</td>
<td>3.1%</td>
<td>7.6%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>0.0%</td>
<td>3.1%</td>
<td>7.6%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3.4%</td>
<td>10.9%</td>
<td>7.6%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4.8%</td>
<td>10.9%</td>
<td>7.6%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1.6%</td>
<td>4.7%</td>
<td>6.1%</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>1.6%</td>
<td>4.7%</td>
<td>6.1%</td>
</tr>
<tr>
<td>Chest pain</td>
<td>1.6%</td>
<td>10.9%</td>
<td>1.5%</td>
</tr>
</tbody>
</table>

1. Treatment emergent adverse events (TEAE) (PT level) reported in 5% or more of patients in either treatment arms (5 or 2.5 mg/kg) and elevated by at least 2-fold over placebo. Source: SUSTAIN Study
## Crizanlizumab is differentiated versus emerging new SCD treatments

<table>
<thead>
<tr>
<th></th>
<th>Crizanlizumab</th>
<th>L-glutamine</th>
<th>GBT440</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism</strong></td>
<td>Inhibits P-selectin</td>
<td>Not fully understood, involved in oxidative damage in RBCs</td>
<td>Hemoglobin S modifier, increasing hemoglobin's affinity for oxygen</td>
</tr>
<tr>
<td><strong>Impact on VOCs</strong></td>
<td>45.3% reduction vs. placebo</td>
<td>25% reduction vs. placebo</td>
<td>Non statistically significant reduction seen in Part A of Ph3 HOPE study(^1)</td>
</tr>
<tr>
<td><strong>Safety profile</strong></td>
<td>Well-tolerated</td>
<td>Concerns for potential long-term risks to renal and hepatic function</td>
<td>Well tolerated</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Intravenous infusion, potential to improve care and compliance due to regular healthcare encounters</td>
<td>Oral powder mixed into suspension, twice daily</td>
<td>Oral pill</td>
</tr>
</tbody>
</table>

---

Crizanlizumab key takeaways

1. VOCs are a major burden and significant unmet need in SCD; more VOC-free days matter to patients and improve quality of life.

2. Crizanlizumab represents a significant opportunity to help SCD patients:
   - Clinically meaningful reduction of VOCs
   - Consistent results across patient subgroups
   - Potential disease-modifying therapy

3. Planned US and EU filings in H1-2019
   - Bridging study in healthy volunteers completed
   - PK/PD study completed enrollment necessary for submission
   - Pediatric study recruiting, with broader clinical plan in progress
Alpelisib (BYL719): potent, specific inhibitor of PI3K-α

Alpelisib specifically inhibits the PI3K-α isoform\(^1,2\), thus avoiding the cumulative toxicity associated with inhibition of all four PI3K isoforms\(^3\)

Alpelisib has demonstrated antitumor activity in a number of cancer cell lines and tumor xenograft models, especially those harboring *PIK3CA* alterations\(^4,5\)

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ER, estrogen receptor; PI3K, phosphatidylinositide 3-kinase; mTOR, mechanistic target of rapamycin; AKT, protein kinase B

Alpelisib SOLAR-1: Ph3 randomized, controlled trial (NCT02437318)

Key eligibility criteria

Men or postmenopausal women, with HR+/HER2- ABC

Recurrence/progression on/after prior AI

Identified PIK3CA status (in archival or fresh tumor tissue)

Measurable disease or ≥1 predominantly lytic bone lesion

ECOG performance status ≤1 (n=572)

PIK3CA-mutant cohort (n=341) 1:1, stratified by presence of liver/lung metastases and prior CDK 4/6 inhibitor treatment

PIK3CA-non-mutant cohort (n=231)

Primary endpoint

PFS (locally assessed) in PIK3CA-mutant cohort

Secondary endpoints include:

OS (PIK3CA-mutant cohort)

PFS (PIK3CA-non-mutant cohort)

PFS (PIK3CA-mutation in ctDNA)

OS (PIK3CA-non-mutant cohort)

ORR

Safety

PIK3CA-mutant cohort

ALP 300 mg QD PO + FUL 500 mg IM\(^1\)

n=169

PBO + FUL 500 mg IM\(^1\)

n=172

PIK3CA-non-mutant cohort

ALP 300 mg QD PO + FUL 500 mg IM\(^1\)

n=115

PBO + FUL 500 mg IM\(^1\)

n=116

ALP=alpelisib; CBR=clinical benefit rate; CT=chemotherapy; ctDNA=circulating tumor DNA; ECOG=Eastern Cooperative Oncology Group; ET=endocrine therapy; FUL=fulvestrant; IM, intramuscular; ORR=overall response rate; OS=overall survival; PBO=placebo; PFS=progression-free survival; PO=orally; QD=daily; R=randomization; ABC=advanced breast cancer; AI=aromatase inhibitor  

Source: Andre F, Ciruelos E, Rubovszky G et al. Alpelisib + fulvestrant for HR+, HER2- advanced breast cancer: Results of the Phase III SOLAR-1 trial. Presented at the European Society for Medical Oncology (ESMO) 2018 Congress (Abstract LBA3_PR) on October 20, 2018  

1. Fulvestrant given on Day 1 and Day 15 of the first 28-day cycle, then Day 1 of subsequent 28-day cycles.
Alpelisib study met primary endpoint of PFS in the PIK3CA-mutant cohort

Overall survival data immature at this time and will be discussed at a later date.

Source: Andre F, Ciruelos EM, Rubovszky G et al. Alpelisib + fulvestrant for HR+, HER2- advanced breast cancer: Results of the Phase III SOLAR-1 trial. Presented at the European Society for Medical Oncology (ESMO) 2018 Congress (Abstract LBA3_PR) on October 20, 2018.
Alpelisib key takeaways

1. Following progression on or after an aromatase inhibitor with or without a CDK 4/6 inhibitor, vs. fulvestrant alone.

~40% of HR+/HER2– breast cancer patients have a PIK3CA mutation, which is associated with poor prognosis; currently there are no treatments that target this mutation.

Alpelisib plus fulvestrant significantly improved PFS and ORR in patients with PIK3CA mutated HR+/HER2- advanced breast cancer

Alpelisib (BYL719) is the first and only investigational alpha-specific PI3K inhibitor to show superior PFS and predictable, manageable tolerability.

Health authority interactions have been initiated and regulatory submissions are planned to start in 4Q-2018.

1. Following progression on or after an aromatase inhibitor with or without a CDK 4/6 inhibitor, vs. fulvestrant alone.
Conclusions

1. Oncology has a portfolio with differentiated medicines and transformational platforms.

2. Crizanlizumab (SEG101) is a promising treatment for patients with sickle cell disease, results from a pivotal trial have shown that it prevents VOCs; US and EU filings planned for 2019.

3. Ph3 studies of canakinumab (ACZ885) in adjuvant NSCLC, 1st line NSCLC, and 2nd line NSCLC are ongoing; canakinumab has the potential to become the new standard of care in these settings.

4. Radioligand therapy platform is broad, with products and indications in development beyond Lutathera® for GEP-NET.

5. Alpelisib (BYL719) is the first and only investigational alpha-specific PI3K inhibitor to show superior PFS and predictable, manageable tolerability.
Appendix
Vaso-occlusive Crisis (VOC) is a major burden to sickle cell disease patients

VOC is #1 cause of hospitalization in sickle cell disease (SCD), with ~200,000 emergency department visits per year in US\(^1,2\)

3 out 5 SCD patients have ≥2 VOC per year\(^3\) despite current standard of care

Every single VOC:
- Worsens patients’ QoL\(^4\)
- Increases risk of organ damage\(^5\) and death\(^6\)

QoL=Quality of life; SCD=Sickle Cell Disease  
\(^3\) Kantar Health Patient Chart Study – Novartis  
\(^5\) Audard V et al Orphanet J Rare Dis. 2014 Apr 29;9:67  
There is a significant unmet need in the care of VOCs despite available treatments

Standard of care for VOCs

**Acute VOC**
- Primarily *symptomatic treatments*, e.g. analgesics, hydration, oxygen, blood transfusions

**Chronic VOC prevention**
- **Hydroxyurea (HU) / hydroxycarbamide (HC)**
  - Limitations may include poor compliance, toxicities
  - Many patients on HU still experience VOCs
- **L-glutamine** (filed in EU, approved in the US)
  - Limitations may include difficulty in managing powder formulation
  - Many patients on L-glutamine still experience VOCs

VOC=Vaso-Occlusive Crisis
**Crizanlizumab: SUSTAIN study design**

**Randomized, double-blind, placebo-controlled, multinational study**

N=198 patients
- Aged 16–65 years, with
- SCD (HbSS, HbSC, HbSβ0 thalassemia or HbSβ+ thalassemia) and
- History of 2–10 VOC leading to health-care visit in the previous 12 months

**Stratification factors:**
- 2-4 vs 5-10 VOC leading to healthcare visit in the year prior to screening
- On or off HU/HC

**50-week treatment**

**Randomization**

- **Crizanlizumab 5.0 mg/kg (n=67)**
- **Crizanlizumab 2.5 mg/kg (n=66)**
- **Placebo (n=65)**

**Primary efficacy endpoint:**
Annual rate of VOC leading to healthcare visit$^2$, adjudicated by independent crisis review committee

**Key secondary endpoint:**
Number of hospitalization days per year

Source: Ataga KI et al. ASH 2016; Abst#92707; Ataga KI et al. N Eng Jour Med. 2017. 1. Patients receiving hydroxyurea or erythropoietin were included if prescribed for the preceding 6 months and dose was stable for at least 3 months. 2. VOC leading to a healthcare visit is defined as an acute episode of pain with no medically determined cause other than a vaso-occlusive event that requires a medical facility visit and treatment with oral or parenteral narcotics, or parenteral non-steroidal anti-inflammatory drugs. Acute chest syndrome, hepatic sequestration, splenic sequestration and priapism (requiring a visit to a medical facility) were also considered VOC leading to a healthcare visit for analysis purposes.
Crizanlizumab generally well tolerated with low incidence of discontinuations due to TEAEs

Overall incidence of TEAEs

<table>
<thead>
<tr>
<th>TEAE Type</th>
<th>Placebo</th>
<th>Crizanlizumab 2.5 mg/kg</th>
<th>Crizanlizumab 5 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td>88.7%</td>
<td>87.5%</td>
<td>86.4%</td>
</tr>
<tr>
<td>Any severe TEAE</td>
<td>19.4%</td>
<td>21.9%</td>
<td>18.2%</td>
</tr>
<tr>
<td>Treatment emergent SAE</td>
<td>27.4%</td>
<td>32.8%</td>
<td>25.8%</td>
</tr>
</tbody>
</table>

Discontinuation due to TEAE:
- Placebo: 4.8%
- Crizanlizumab 2.5 mg/kg: 1.6%
- Crizanlizumab 5 mg/kg: 3.0%

TEAE – Treatment emergent adverse events  Source: SUSTAIN Study
Alpelisib, promising addition to portfolio, strengthening presence in HR+/HER2- breast cancer

<table>
<thead>
<tr>
<th>HR-</th>
<th>HR+</th>
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<tbody>
<tr>
<td>HER2-</td>
<td>HR-/HER2-~75K patients (~10%)</td>
</tr>
<tr>
<td>HER2+</td>
<td>HER2+~110K patients (~20%)</td>
</tr>
<tr>
<td>HR+/HER2-~380K patients (~70%)</td>
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</table>

Alpelisib (α-specific PI3K inhibitor):
- Prevalence of PIK3CA mutation is in approximately 40% of HR+/HER2- advanced breast cancer patients
- Alpelisib potentially represents an important therapy for patients with tumors harboring PIK3CA mutations

Source: Kantar 2017, G7 patients estimates.
Alpelisib adverse events; safety profile manageable

<table>
<thead>
<tr>
<th>AEs ≥20% in either arm, %</th>
<th><strong>Alpelisib + fulvestrant N=284</strong></th>
<th><strong>Placebo + fulvestrant N=287</strong></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Grade 3</td>
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<tr>
<td>Any adverse event</td>
<td>282 (99.3)</td>
<td>183 (64.4)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>181 (63.7)</td>
<td>93 (32.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>164 (57.7)</td>
<td>19 (6.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>127 (44.7)</td>
<td>7 (2.5)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>101 (35.6)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Rash</td>
<td>101 (35.6)</td>
<td>28 (9.9)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>77 (27.1)</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Decreased weight</td>
<td>76 (26.8)</td>
<td>11 (3.9)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>70 (24.6)</td>
<td>7 (2.5)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>69 (24.3)</td>
<td>10 (3.5)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>58 (20.4)</td>
<td>5 (1.8)</td>
</tr>
</tbody>
</table>

Hyperglycemia was the most frequent AE leading to treatment discontinuation (18 patients [6.3%] in the alpelisib arm and no patients in the placebo arm).

19 on-treatment deaths were observed; 7 (2.5%) and 12 (4.2%) in the alpelisib and placebo arms, respectively. 2 in alpelisib arm and 4 in placebo arm died due to causes other than study indication (all were unrelated to study treatment).

Source: Andre F, Ciruelos EM, Rubovszky G et al. Alpelisib + fulvestrant for HR+, HER2- advanced breast cancer: Results of the Phase III SOLAR-1 trial. Presented at the European Society for Medical Oncology (ESMO) 2018 Congress (Abstract LBA3_PR) on October 20, 2018.
## Agenda

<table>
<thead>
<tr>
<th>Timing</th>
<th>Q&amp;A</th>
<th>Session</th>
<th>Presenters</th>
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</thead>
<tbody>
<tr>
<td>12:00 – 13:00</td>
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<td>Registration / light lunch</td>
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<tr>
<td>13:00</td>
<td></td>
<td>Opening</td>
<td>Samir Shah</td>
</tr>
<tr>
<td>13:00 – 13:20</td>
<td>5 min</td>
<td>Pipeline, platforms</td>
<td>John Tsai</td>
</tr>
<tr>
<td>13:20 – 14:20</td>
<td>30 min</td>
<td>AveXis AVXS-101</td>
<td>Dave Lennon, Brian Kaspar</td>
</tr>
<tr>
<td>14:20 – 15:15</td>
<td>30 min</td>
<td>Oncology Radioligand therapies, ACZ885 in NSCLC, SEG101, BYL719</td>
<td>Liz Barrett, Samit Hirawat</td>
</tr>
<tr>
<td>15:15 – 15:45</td>
<td></td>
<td>Break</td>
<td></td>
</tr>
<tr>
<td>15:45 – 16:45</td>
<td>30 min</td>
<td>Upcoming launches (late-stage pipeline) QAW039, RTH258, BAF312, OMB157</td>
<td>John Tsai, Danny Bar Zohar, Paul Hudson</td>
</tr>
<tr>
<td>16:45 – 17:15</td>
<td>10 min</td>
<td>Near term value drivers Cosentyx®, Entresto®, Gilenya®</td>
<td>Paul Hudson, John Tsai</td>
</tr>
<tr>
<td>17:15 – 17:30</td>
<td>15 min</td>
<td>Q&amp;A session</td>
<td>Vas Narasimhan, Harry Kirsch, John Tsai, Paul Hudson, Liz Barrett</td>
</tr>
<tr>
<td>17:30</td>
<td></td>
<td>Cocktail</td>
<td>All</td>
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</tbody>
</table>
Fevipiprant (QAW039)
“Silent treatment gap” of 3m patients whose asthma remains unresolved despite availability of injectable biologics

5 million moderate-to-severe asthma\(^1\) patients in the US

Managed by a combination of inhaled therapies

Unresolved symptoms and exacerbations on inhaled SoC

Patients treated with inhaled therapies and injectable biologics

5m

3m

120k

\(^1\) Moderate to Severe refers to patients on GINA step 4/5 therapies (i.e ICS/LABA ± LAMA)

Sources: CDC: US claims data
Oral fevipiprant (QAW039) blocks the DP2 pathway, a principal regulator of the asthma inflammatory cascade

By analogy with other prostaglandin receptors, DP2 is now the IUPHAR\(^1\) recommended name for the receptor previously known as CRTh2. Reinforced by general trend in literature to reference new nomenclature (DP2)

Fevipiprant has superior potency, high selectivity, clean safety profile

### Ki (nM)

<table>
<thead>
<tr>
<th>Receptor affinity</th>
<th>Fevipiprant</th>
<th>AZD-1981</th>
<th>Setipiprant</th>
<th>BI-617800</th>
<th>Timapiprant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T½ (mins)</strong></td>
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<tr>
<td>Fevipiprant</td>
<td>1.1</td>
<td>3.2</td>
<td>4.4</td>
<td>7.2</td>
<td>4.5</td>
</tr>
<tr>
<td>AZD-1981</td>
<td></td>
<td>1.3</td>
<td>4.4</td>
<td>7.2</td>
<td>4.5</td>
</tr>
<tr>
<td>Setipiprant</td>
<td></td>
<td></td>
<td>0.8</td>
<td>0.6</td>
<td>0.4</td>
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<tr>
<td>BI-617800</td>
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<tr>
<td>Timapiprant</td>
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</table>

**Superior potency**
- Lower Ki value and higher T½ value indicate better potency.

**High selectivity**
- No activity (IC$_{50}$ > 10 µM) vs. DP1 receptor and 190 additional molecular targets
- Intact DP1 signaling is important for antiviral immunity and vasodilation

**Clean safety profile**
- >2,700 patients exposed to Fevipiprant in ongoing clinical program
- No significant safety signals detected in phase 2 and the ongoing phase 3 program

Note: Sykes D et al; Fevipiprant (QAW039), a Slowly Dissociating CRTh2 Antagonist with the Potential for Improved Clinical Efficacy. Mol Pharmacol 2016; 89:593–605
Fevipiprant efficacy increases with asthma severity: Moderate-severe asthma population selected for Ph 3

### FEVIPIPRANT PHASE 2 PROGRAMS

<table>
<thead>
<tr>
<th>MILD</th>
<th>MODERATE</th>
<th>MODERATE TO SEVERE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PoC: A2201&lt;sup&gt;1&lt;/sup&gt;</td>
<td>DRF: A2206&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Mechanistic: A2208&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>500mg (total daily dose)</td>
<td>Significant ↑ in FEV₁ of &gt;112 ml above placebo</td>
<td>Significant decrease of sputum eosinophils (72%), comparable to biologics</td>
</tr>
<tr>
<td>Overall population, no effect</td>
<td>150 mg QD provided optimal effect</td>
<td>450 mg daily dose</td>
</tr>
<tr>
<td>Subgroup analysis: highest efficacy (FEV₁ increase) observed in patients with lower lung function at baseline (Predicted FEV₁ &lt;70%)</td>
<td>QD and BID dosing similar</td>
<td>Efficacy on ACQ&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td>Change vs. placebo (mL) P = 0.002</td>
<td>207</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>&lt;80%</td>
<td>&lt;75%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HIGH EOS&lt;sup&gt;*&lt;/sup&gt;</th>
<th>LOW EOS&lt;sup&gt;*&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 2 data consistent with published data identifying upregulation of PGD2 pathway in patients with severe, poorly controlled, asthma&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Other DP2 programs only focused on mild and moderate patients</td>
</tr>
</tbody>
</table>

*High eos is defined as sputum eosinophils ≥2% (A2208 patient population).

Sources:
5. Asthma Control Questionaire
Fevipiprant reduced sputum eosinophils to biologic levels providing confidence for Ph3 exacerbation reduction.

Placebo-adjusted reduction in sputum eosinophils (% reduction)
Cross Study Comparisons

Fevipiprant\(^1\)
- 72% REDUCTION

57% reduction with Mepolizumab\(^2\)

70% reduction with Benralizumab\(^3\)

High sputum eosinophils are a recognized predictor of exacerbations and poor control in asthma.

Mepolizumab and Benralizumab significantly decreased airway sputum eosinophils in Ph2/3 and reduced exacerbations in Ph3 studies.

Fevipiprant demonstrates similar drop in sputum eosinophils in Ph2 studies supporting expectations for significant exacerbation reduction in Ph3.

Fevipiprant also demonstrated efficacy across key clinical endpoints, including lung function, symptom control, QoL.

---

Fevipiprant development: targeting biologic efficacy with oral simplicity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Targeted efficacy profile</th>
<th>Exacerbation reduction</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>% reduction over 52 weeks</td>
<td></td>
</tr>
<tr>
<td>Fevipiprant¹</td>
<td>30</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Benralizumab²</td>
<td>28</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>Mepolizumab³</td>
<td>42</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Reslizumab⁴</td>
<td>50</td>
<td>59</td>
<td></td>
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<tr>
<td>Dupilumab⁵</td>
<td>46</td>
<td>67</td>
<td></td>
</tr>
</tbody>
</table>

1. Fevipiprant: Study defines high eosinophil levels ≥250 cells/µL. Targeted efficacy profile studied with GINA step 4/5 patients.  
### Asthma Ph3 program (>4,500 patients) on track for worldwide regulatory submissions 2020

<table>
<thead>
<tr>
<th>Trial</th>
<th>Asthma population</th>
<th>Primary endpoint</th>
<th>Study rationale</th>
<th>Next milestone</th>
</tr>
</thead>
</table>
| **Luster** | Moderate to Severe (GINA 4/5) Age ≥ 12 years | **Exacerbations**  
1) High eosinophil  
2) All patients | Core registration study | First results 2H2019 |
| **Spirit** | Moderate to Severe (GINA 3/4/5) Age ≥ 12 years | **Safety** | Core registration study | Fully enrolled 2019 Interim Analysis 2H2019 |
| **Zeal** | Moderate (GINA 3/4) Age ≥ 12 years | **Lung Function** (FEV1) | Supportive study | Fully enrolled 2019 Results 2020 |

Note: Study treatment durations are LUSTER (52 weeks), SPIRIT (>52 weeks), ZEAL (12 weeks). In addition, pediatric studies will be conducted as a regulatory commitment.  
1. Study defines high eosinophil levels ≥250 cells/µL.
Fevipiprant, potentially the first oral DP2 receptor antagonist, with compelling base case and significant upside potential in asthma...

Outcomes to ongoing fevipiprant Ph3 asthma studies; US patient numbers (≥12 years old)

<table>
<thead>
<tr>
<th>ASTHMA SEVERITY</th>
<th>BASE CASE: LUSTER trials positive in high eosinophilic** patients</th>
<th>LUSTER trials positive in all patients (high &amp; low eos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate (GINA 3)</td>
<td>1.4 MILLION PATIENTS</td>
<td>1.5 MILLION PATIENTS</td>
</tr>
<tr>
<td>Moderate-to-severe (GINA 4/5)</td>
<td>~400k of these patients meet LUSTER patient entry criteria¹</td>
<td></td>
</tr>
</tbody>
</table>

1. ≥2 exacerbations in last 12 months.
2. High eosinophils defined as ≥ 250 cells/µL.
3. 1.4mn patients in GINA 3 have unresolved symptoms and exacerbations on GINA 3 regimes
... and significant potential in a broad range of indications beyond asthma, driven by DP2 science

<table>
<thead>
<tr>
<th>Under development in asthma for special populations</th>
<th>Evaluating additional Respiratory indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficult to treat asthma populations</td>
<td></td>
</tr>
<tr>
<td>Pediatric (1 to &lt; 12 years)</td>
<td>Severe Allergic Rhinitis</td>
</tr>
<tr>
<td></td>
<td>COPD</td>
</tr>
<tr>
<td></td>
<td>Nasal polyposis</td>
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</tbody>
</table>
Brolucizumab (RTH258)
Fluid recurrence is a key measure of AMD disease activity for retinal specialists

What is the most important factor indicating recurrent wet AMD disease activity in the maintenance phase?

- Recurrence of Subretinal Fluid: 54.0% (International), 54.0% (US)
- Recurrence of Intraretinal Fluid: 24.4% (International), 24.4% (US)
- Macular Hemorrhage: 9.1% (International), 10.9% (US)
- Loss of Vision: 4.9% (International), 10.5% (US)
- Other: 1.7% (International), 4.0% (US)
- Pigment Epithelial Detachment (PED): 0.3% (International), 0.0% (US)

1. American Society of Retina Specialists (ASRS) Preferences and Trends (PAT) membership survey 2018
Brolucizumab maintained robust vision gains through year 2

Full Analysis Set, LOCF. Mean differences in BCVA (brolucizumab–aflibercept, Δ). *Non-inferiority (NI) margin = 4 letters. Analyzed using ANOVA model with baseline BCVA categories (<55, 56-70, >=71 letters), age categories (<75,≥75 years) and treatment as fixed effect factors. BCVA, best corrected visual acuity; LOCF, last observation carried forward; LS, least squares; SE, standard error
Brolucizumab achieved superior reductions in CST from baseline to Week 16 and Week 48; difference maintained at Week 96

Matched Phase

Maintenance Phase

<table>
<thead>
<tr>
<th>Week</th>
<th>Matched Phase</th>
<th>Maintenance Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL</td>
<td>brolucizumab 3 mg (n = 358)</td>
<td>brolucizumab 6 mg (n = 360)</td>
</tr>
<tr>
<td></td>
<td>brolucizumab 3 mg (n = 358)</td>
<td>aflibercept 2 mg (n = 360)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Change from baseline in CST, LS mean (SE)</th>
<th>P</th>
<th>P</th>
<th>P</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>BL</td>
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<td>96</td>
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</table>

Full Analysis Set, LOCF. Prespecified secondary endpoint in both HAWK and HARRIER. Confirmatory superiority analysis at Week 16 and Week 48 in HAWK only. 1-sided p-values for HAWK; for confirmatory superiority testing in HAWK, 1-sided p-values below the adjusted significance level (to account for multiplicity) of P<0.005 (for CST) are regarded as statistically significant. P-values at Week 96 are descriptive. a brolucizumab 3 mg vs aflibercept 2 mg; b brolucizumab 6 mg vs aflibercept 2 mg. BL, baseline; CST, central subfield thickness; LOCF, last observation carried forward; LS, least squares; SE, standard error
## Two-year data reaffirm superiority in key secondary endpoints from year one versus aflibercept in patients with nAMD

<table>
<thead>
<tr>
<th>brolucizumab&lt;sup&gt;1&lt;/sup&gt;</th>
<th>aflibercept&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Visual acuity</strong></td>
<td></td>
</tr>
<tr>
<td>Non-inferior to aflibercept in BCVA change from baseline to Week 48&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>Non-inferior to ranibizumab in the proportion of patients maintaining vision at Week 52</td>
</tr>
<tr>
<td><strong>Anatomical outcomes</strong></td>
<td></td>
</tr>
<tr>
<td>▪ Significantly fewer patients with IRF and/or SRF at Weeks 16 and 48&lt;sup&gt;‡&lt;/sup&gt;; difference maintained at Week 96&lt;sup&gt;†&lt;/sup&gt;</td>
<td>In the clinical studies anatomic measures of disease activity improved similarly in all treatment groups from baseline to week 52</td>
</tr>
<tr>
<td>▪ Superior reductions in CST at Weeks 16 and 48&lt;sup&gt;‡&lt;/sup&gt;; difference maintained at Week 96&lt;sup&gt;†&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>▪ Fewer patients with sub-RPE fluid at Weeks 16&lt;sup&gt;‡&lt;/sup&gt;, 48&lt;sup&gt;‡&lt;/sup&gt;, and 96&lt;sup&gt;†&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>▪ Significantly fewer patients with disease activity at Week 16&lt;sup&gt;†&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>q12w dosing</strong></td>
<td></td>
</tr>
<tr>
<td>▪ &gt;50% of patients maintained on q12w interval after loading through Week 48</td>
<td>Although not as effective as the recommended every 8 week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy</td>
</tr>
<tr>
<td>▪ Over 75% of those who completed Week 48 on a q12w interval were maintained on q12w interval until Week 96</td>
<td></td>
</tr>
</tbody>
</table>

*Prespecified secondary endpoint in both HAWK and HARRIER, with confirmatory superiority analysis in HAWK only. †Primary endpoint; ‡Descriptive P-values at Week 96 related to prespecified secondary endpoints assessed at Weeks 16 and 48. §Prespecified secondary endpoint in both HAWK and HARRIER. 1. Data on file, HAWK & HARRIER Ph3. 2. Eylea [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc. 2018. BCVA, best corrected visual acuity; CST, central subfield thickness; IRF, intraretinal fluid; RPE, retinal pigment epithelium; SRF, subretinal fluid.
Brolucizumab has the potential to address important unmet needs in nAMD - dries better

Less retinal fluid\(^1\)  \hspace{2cm} Less injections\(^2\)  \hspace{2cm} Uncompromised vision\(^3\)

*Illustrative

1. At Week 48, demonstrated superiority in three secondary endpoints considered key markers of nAMD in clinical practice: central subfield retinal thickness, retinal fluid (intraretinal fluid and/or subretinal fluid) and disease activity; advantages maintained at Week 96.
2. At Week 48, the majority of patients (56% and 51%) were maintained on q12w injection interval in Hawk and Harrier respectively with remaining patients on q8w regimen (key secondary endpoints); greater than 75% of these patients continued on q12w dosing up to Week 96.
3. Met primary efficacy endpoint of noninferiority to aflibercept in mean change in BCVA with comparable safety to aflibercept; vision gains comparable to aflibercept up to Week 96.

Mayzent™ (siponimod, formerly BAF312) and Ofatumumab (OMB157)
Our leading MS portfolio is supported by cutting edge innovation

- Progression is recognized to start earlier than previously thought
- Patient relevant outcomes measured digitally is the expectation
- Real-world data and advanced analytics used to gain insights and inform decisions
- Potential biomarkers, beyond MRI are becoming more accessible

2. The brand name MayzentTM has been provisionally approved by the FDA and EMA for the investigational product siponimod (BAF312), but the product itself has not been approved for sale in any country.

NfL: Neurofilament light chain, SC: subcutaneous
Mayzent™ (siponimod, formerly BAF312)
Delay progression, EXPAND possibilities

The brand name Mayzent™ has been provisionally approved by the FDA and EMA for the investigational product siponimod (BAF312), but the product itself has not been approved for sale in any country.
Majority of RMS patients transition to SPMS but are we diagnosing them too late?¹⁻³

50-80% of patients progress to SPMS⁴,⁵,⁶: ~362k in U.S & EU⁷

Unprecedented efficacy of siponimod in EXPAND is expected to break the status quo and drive urgency to identify SPMS earlier

70% of patients received SPMS diagnosis at EDSS ≥ 6
76% of patients had progression recognized at EDSS ≤ 3
84.8% of patients had onset of progression at EDSS ≤ 2

Diagnosed SPMS with or without relapses\(^2\)
Irreversible loss of physical and cognitive function, independent of relapses.
Worsening MS symptoms with decline in active disease & relapses.

~230K pts US & EU5

MS with signs of increased disability progression\(^2\)
Symptoms worsen in a "softer" manner despite treatment, more relapses don't return to baseline, signaling neurodegenerative decline or progressive disease.

~132K pts US & EU5

Siponimod (BAF312) a highly selective S1P\textsubscript{1,5} with a unique and well characterized profile

**Comparison of S1P receptor modulators profiles\textsuperscript{7}**

<table>
<thead>
<tr>
<th></th>
<th>Gilenya\textsuperscript{®} (Fingolimod) Marketed\textsuperscript{*}</th>
<th>Ozanimod Phase 3 complete</th>
<th>Siponimod Phase 3 complete</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studied Phase 3 population</td>
<td>RMS \textsuperscript{*}</td>
<td>RMS</td>
<td>SPMS</td>
</tr>
<tr>
<td>Receptor selectivity</td>
<td>S1P\textsubscript{1,3,4,5}</td>
<td>S1P\textsubscript{1,5}</td>
<td>S1P\textsubscript{1,5}</td>
</tr>
<tr>
<td>Activity of metabolites</td>
<td>Fingolimid-P; active at S1PRs</td>
<td>Metabolites, active at S1PRs</td>
<td>None</td>
</tr>
<tr>
<td>Elimination Half life of parent compound (hrs)\textsuperscript{7}</td>
<td>180h</td>
<td>19h; (CC-112273; 10-13 days\textsuperscript{8})</td>
<td>30h</td>
</tr>
<tr>
<td>HR reduction upon Treatment initiation</td>
<td>(no titration) -7.4bpm @4-5h</td>
<td>Dose titration over 7d -5-8bpm nadir @day8</td>
<td>Dose titration over 5d -3bpm @day7</td>
</tr>
</tbody>
</table>

\textsuperscript{*}Gilenya is approved for RMS for adults and pediatric patients, PPMS study did not meet the primary end point

\textsuperscript{1}SIP1.5, sphingosine 1-phosphate receptors subtypes 1 and 5


\textsuperscript{3}Seabrook TJ, et al. Mult Scler. 2010;16:P856

\textsuperscript{4}Briard E, et al. ChemMedChem. 2015;10:1008–1018

\textsuperscript{5}Mannioui A, et al. Mult Scler. 2017 [Epub ahead of print]


\textsuperscript{8}Disclosed at Celgene Q1 2018 Investors Call, May 4th, 2018
EXPAND: the largest Ph3 study in a typical SPMS population

Randomized, double-blind, placebo-controlled, event- and exposure-driven study\(^1\)

EXPAND study was conducted across 31 countries and 292 sites

**EXPAND Ph3 population is typical SPMS and significantly differs from the other RMS trials**

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>SPMS</th>
<th>Recent RMS trials (2010-2015)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EXPAND(^1) Siponimod</td>
<td>DEFINE(^2) DMF</td>
</tr>
<tr>
<td>Number of patients</td>
<td>1651</td>
<td>1237</td>
</tr>
<tr>
<td>Age, years (mean)</td>
<td>48</td>
<td>38</td>
</tr>
<tr>
<td>Time since onset, years (mean)</td>
<td>17</td>
<td>5.6(^#)</td>
</tr>
<tr>
<td>EDSS (mean/median)</td>
<td>5.4/6.0</td>
<td>2.4/n.r.(^#)</td>
</tr>
<tr>
<td>EDSS ≥ 6.0 (%)</td>
<td>56</td>
<td>0(^#)</td>
</tr>
<tr>
<td>Timed 25-foot walk test, mean (sec)</td>
<td>16.7</td>
<td>n.r.</td>
</tr>
<tr>
<td>% of patients with Gd(^+) lesions</td>
<td>21</td>
<td>n.r.</td>
</tr>
<tr>
<td>T2 lesion load, mean (cm(^3))</td>
<td>15</td>
<td>n.r.</td>
</tr>
<tr>
<td>Relapse-free for prior 2 years, (%)</td>
<td>64</td>
<td>0(^#)</td>
</tr>
<tr>
<td>On-study relapses (% in comparator group)</td>
<td>19(^#)</td>
<td>46(^$)</td>
</tr>
<tr>
<td>On-study ARR (comparator group)</td>
<td>0.16(^$)</td>
<td>0.36(^$)</td>
</tr>
</tbody>
</table>

EXPAND data suggest meaningful efficacy of siponimod on a variety of measures relevant for SPMS\(^1\),\(^2\)

<table>
<thead>
<tr>
<th>Physical disability outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time to 25 Feet Walk: 3-month confirmed ≥20% worsening</strong></td>
</tr>
<tr>
<td><strong>MS Walking Scale-12 (PRO)(^a)</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cognitive disability outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Change from baseline in Symbol Digit Modalities Test (SDMT)(^2)</strong></td>
</tr>
<tr>
<td><strong>Risk of 6-month confirmed worsening of ≥4 points on SDMT (post-hoc)</strong></td>
</tr>
</tbody>
</table>

**Acute clinical relapses**

- Annualized relapse rate: 55.5% | <0.0001

**Brain imaging outcomes\(^*\)**

- **Change from baseline in T2 Lesion Volume\(^*\)**: 79.1% | <0.0001
- **Number of Gd+ lesions/per scan\(^b\)**: 86.3% | <0.0001
- **Number of new or newly enlarging T2 lesions\(^c\)**: 80.6% | <0.0001
- **Percent brain volume change\(^c\)**: 23.4% | 0.0002

---

\(^a\)Primary analysis: time to 3-month CDP on Full Analysis Set (FAS) without imputation for missing data; FAS=all treated patients analyzed according to randomization; \(^b\)Cox proportional hazards model with treatment, country/region, baseline EDSS, and SPMS group (with/without superimposed relapses, baseline definition) as covariates. CI, confidence interval; CDP, confirmed disability progression; HR, hazard ratio  
\(^c\)Gd+, gadolinium-enhancing; SDMT, Symbol Digit Modalities Test; T2LV, T2 lesion volume; T25FW, timed 25-foot walk test  
\(^*\)Difference in change from baseline in adjusted means; \(^\text{Cumulative number of Gd-enhancing T1 lesions per scan up to and including Month 24}  
\(^\text{Average change over Months 12 and 24, relative to previous scan}  
\(^\text{Difference in change from baseline in adjusted means over Month 12 and 24}  

---

Novartis R&D and investor update | November 5, 2018
Siponimod is the only DMT that demonstrated efficacy in a typical SPMS population

### Typical SPMS

<table>
<thead>
<tr>
<th></th>
<th>EXPAND¹ Siponimod</th>
<th>ASCEND² Natalizumab</th>
<th>N.American³ IFNB1b study</th>
<th>European⁴ IFN1b study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>1651</td>
<td>887</td>
<td>939</td>
<td>718</td>
</tr>
<tr>
<td>Age, years (mean)</td>
<td>48</td>
<td>47</td>
<td>47</td>
<td>41</td>
</tr>
<tr>
<td>Time since onset, years (mean)</td>
<td>17</td>
<td>17</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>EDSS (mean/median)</td>
<td>5.4/6.0</td>
<td>5.6/6.0</td>
<td>5.1/n.r.</td>
<td>5.2</td>
</tr>
<tr>
<td>On-study ARR (placebo group)</td>
<td>0.16</td>
<td>0.17</td>
<td>0.28</td>
<td>0.64</td>
</tr>
</tbody>
</table>

**Primary Endpoint**

<table>
<thead>
<tr>
<th></th>
<th>EXPAND¹ Siponimod</th>
<th>ASCEND² Natalizumab</th>
<th>N.American³ IFNB1b study</th>
<th>European⁴ IFN1b study</th>
</tr>
</thead>
<tbody>
<tr>
<td>3mCDP: 21%↓ (p=0.0130)</td>
<td>6mCDP: 26%↓</td>
<td>Composite²: OR 0.86 (p=0.287)</td>
<td>6mCDP: hazard ratio not reported, p=0.71</td>
<td>3mCDP, OR 0.65, p=0.0008</td>
</tr>
<tr>
<td>6mCDP: 26%↓ (p=0.006)</td>
<td></td>
<td>[6mCDP: OR 1.06 (p=0.753)]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CDP, confirmed disease progression; OR, odds ratio, ARR, annualized relapse rate; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; n.r, not reported; IFN1b, interferon-beta1b

2. Kapoor R, et al. Lancet Neurol. 2018;17:405-15 (composite endpoint included time to EDSS progression, 20% increase in timed 25 foot walk or 20% increase in 9-hole Peg test)
Additional analysis: disentangling the effect on disability progression from relapses

Siponimod efficacy in EXPAND was largely independent of relapses

...during the study*

<table>
<thead>
<tr>
<th>3-month confirmed disability progression</th>
<th>Risk ratio (95% CrI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months</td>
<td>0.80 (0.56; 1.08)</td>
</tr>
<tr>
<td>18 months</td>
<td>0.86 (0.57; 1.24)</td>
</tr>
<tr>
<td>24 months</td>
<td>0.82 (0.48; 1.32)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6-month confirmed disability progression</th>
<th>Risk ratio (95% CrI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months</td>
<td>0.67 (0.44; 0.93)</td>
</tr>
<tr>
<td>18 months</td>
<td>0.71 (0.42; 1.09)</td>
</tr>
<tr>
<td>24 months</td>
<td>0.71 (0.37; 1.21)</td>
</tr>
</tbody>
</table>

...before the study

3-month confirmed disability progression (FAS)

<table>
<thead>
<tr>
<th>Overall population</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superimposed relapses</td>
<td></td>
</tr>
<tr>
<td>In the 2 years before study</td>
<td>0.79</td>
</tr>
<tr>
<td>In the year before study</td>
<td>0.67</td>
</tr>
<tr>
<td>No superimposed relapses</td>
<td></td>
</tr>
<tr>
<td>In the 2 years before study</td>
<td>0.87</td>
</tr>
<tr>
<td>In the year before study</td>
<td>0.82</td>
</tr>
</tbody>
</table>

6-month confirmed disability progression (FAS)

<table>
<thead>
<tr>
<th>Overall population</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superimposed relapses</td>
<td></td>
</tr>
<tr>
<td>In the 2 years before study</td>
<td>0.74</td>
</tr>
<tr>
<td>In the year before study</td>
<td>0.63</td>
</tr>
<tr>
<td>No superimposed relapses</td>
<td></td>
</tr>
<tr>
<td>In the 2 years before study</td>
<td>0.70</td>
</tr>
<tr>
<td>In the year before study</td>
<td>0.82</td>
</tr>
</tbody>
</table>

*Definition as per EXPAND protocol 1

1. Reference: B Cree, et al. Progressive MS Therapies and Age-Dependent Factors in MS Therapy Session S8.005 (April 22, 2018), AAN Los Angeles

n=number of subjects with events/N'=number of subjects included in the population.  
FAS, full analysis set
EXPAND safety data was in line with S1P receptor modulation

- Safety profile of siponimod was overall in line with the well established S1P receptor modulator, fingolimod.

- Headache, nasopharyngitis, UTI, and falls – most common adverse events in both treatment groups.

- Frequency of infections, malignancies and deaths did not increase with siponimod versus placebo.

- Most adverse events were of mild-moderate severity & either treatable or resolve on discontinuation.

- First dose effects: dose titration over 5 days mitigated transient heart rate effects on treatment initiation.

- Siponimod long-term data (up to 6 years) did not reveal an increased incidence of AEs over time.

---

In partnership with MS experts, we developed a new easy-to-use, office-based tool to assist in diagnosis and uncover SPMS before it is too late.

- **Patient and Clinician interviews**
  Analysis of difference RRMS vs SPMS in RWE dataset (> 3000pts) Simsek D; ECTRIMS 2015, Zimensen T, AAN 2016

- **Clinicians to rank & weight variables**
  Determine concordance level
  Piani Maijer D, ECTRIMS 2017

- **Validation study ~200**
  (RRMS, SPMS, pts in transition)
  Sensitivity and specificity confirmation. Completion Nov 2018

**SPMS Diagnosis assist tool**
Global rollout 2019

- Raise SPMS awareness
- Mobilize and engage community
- Data insights
Siponimod regulatory activities

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NDA accepted</strong></td>
<td><strong>MAA validated</strong></td>
<td><strong>Fast Track</strong></td>
<td><strong>On Track for Q4</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Designation granted</strong></td>
<td>2018 submission</td>
</tr>
<tr>
<td><strong>PDUFA expected</strong></td>
<td></td>
<td><strong>On track for Q4 2018 submission</strong></td>
<td></td>
</tr>
<tr>
<td><strong>end of March 2019</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>(PRV used)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>latest by Dec 2019</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>On track for Q4 2018 submission</strong></td>
<td></td>
</tr>
</tbody>
</table>
In summary, Mayzent™ delays progression in patients with typical SPMS

- The only investigational DMT that showed efficacy on a variety of measures in typical SPMS patients.
- A next generation S1P receptor modulator; a mitigated first dose HR effect, fast lymphocyte recovery\(^1,2,3\) and no active metabolites.
- With unprecedented EXPAND data\(^3\), patients who have been considered as “core SPMS” (EDSS ~4.5-5.0) as well as those who only start showing signs of progression independent of relapses are expected to benefit from Mayzent™.

---

2. First dose monitoring requirements under health authority review

The brand name Mayzent™ has been provisionally approved by the FDA and EMA for the investigational product siponimod (BAF312), but the product itself has not been approved for sale in any country.
Ofatumumab (OMB157), V 2.0 B-Cell therapy in development for all RMS patients
Target ofatumumab patient population

OFA patients

1st line for RMS pts and as early efficacy switch

Note: this is a fictional patient

Early RMS patient

Age: 24 years
Previous therapy: None
Time since first symptoms: 1 year
Relapses: 1 relapse, EDSS: 0.5
MRI: 1 Gd+ lesion or T2 lesion

Note: this is a fictional patient

Efficacy switch patient

Age: 36 years.
Previous therapy: Teriflunomide
Time since first symptoms: 8 years
Relapses: 1 relapse in 12M, EDSS: 1.5
MRI: Growing number of Gd+ lesions

Note: this is a fictional patient
Ofatumumab: B-cell therapy expected to deliver high efficacy and improved safety from the start without trade-offs

1. High efficacy at low dose

2. Faster B-Cell repletion and potential preserved immunity

3. Potential for lowest immunogenicity

4. Tailored B-cell Tx for RMS patients

- Fully Human mAb
- Low Dose s.c. dosing
- At Home injections
- No Pre-medication

1. Poster presented at ECTRIMS 2017, Paris, France
Ofatumumab: B-cell therapy expected to deliver high efficacy and improved safety from the start without trade-offs

More potent B-CELL LYSIS

Targeted to the B-CELLS that drive MS

PARTIALLY SPARING the ones needed FOR IMMUNE PRESERVATION
Ofatumumab lyses B-Cells more potently

- Ofatumumab binds to unique epitopes on CD20

<table>
<thead>
<tr>
<th>Ab, antibody; aCD20, anti-CD20; EC50, concentration of a drug that gives half-maximal response; FACS, fluorescence-activated cell sorting.</th>
<th>Ofatumumab binds to unique epitopes on CD20</th>
<th>Ofatumumab lyses B-Cells more potently</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCR, ocrelizumab; OFA, ofatumumab; RTX, rituximab; Ubli, ubliliximab</td>
<td>Ofatumumab lyses B-Cells more potently</td>
<td>Ofatumumab lyses B-Cells more potently</td>
</tr>
</tbody>
</table>

OCR, ocrelizumab; OFA, ofatumumab; RTX, rituximab; Ubli, ubliliximab

Significantly lower doses of ofatumumab resulted in similar efficacy in Ph2 (MIRROR study)

1. Hauser et al., NEJM, 359; 7, February 14, 2008
2. Kappos et al., Lancet 2011; 378: 1779-87
3. Bar-Or et al., April 2018, Neurology, 2018; 90:e1805-e1814
Clinical, modelling and preclinical data suggest ofatumumab has faster B-cell repletion and potential for preserved immunity

- Subcutaneous administration could be important and advantageous as compared to intravenous infusions as:
  - Lymph nodes, where MS antigen presentation occurs, are mainly targeted
  - Splenic marginal zone B-cells, responsible for host defense, are partially spared

Please refer to slides 141-143 in backup

Reference: Marina Savelieva et al., poster presentation at ECTRIMS 2017; Paul Smith et al.; AAN 2017 scientific presentation
ASCLEPIOS Ph3 program in RMS

Phase 3 studies
fully recruited as of Q1 2018

Primary Endpoint: Annualized Relapse Rate
Secondary Endpoints: Time to 3M disability progression (CDP); time to 6M CDP; time to 6M confirmed disability improvement (CDI) Gd enhancing T1 lesions; New or enlarging T2 lesions; Brain volume loss; Serum neurofilaments (NFL).

Study duration: Event driven study.
A blinded sample size re-assessment in Q1’19 will determine the end of study timing.

D, day; EDSS, Expanded Disability Status Scale; M, month; MS, multiple sclerosis; s.c., subcutaneous, CDP – confirmed disability progression, CDI confirmed disability improvement. 1. Hauser S. et al, Platform presentation, AAN 2017, April 22-26, Boston, USA
Appendix
Novartis database contains high quality clinical and biomarker data from more than 32,000 MS patients across all age groups and types of MS.

Using advanced data and image analytics we aim to re-characterize MS, potentially:
- Enable more accurate identification of responders to our therapies
- Understand when progression starts
- De-risk future trials

### Neurofilament light chain (NFL)

- **Specific to neurons**: NFL is polymer specific to neurons and can be detected in the blood upon damage to nerve cells\(^1,2\).
- **Tightly linked**: NFL is tightly linked to MRI lesion measures (T1, T2), relapses and future brain atrophy as well as to short and long-term clinical outcomes in MS.
- **High specificity and sensitivity**: NFL’s high specificity and sensitivity could allow it to serve as a more sensitive measure to detect disease activity even in the absence of MRI activity\(^3,4\).

---

4. Kuhle et al., Neurol.; under review  
5. Adapted from Khalil M, et al. *Nat Rev Neurol* 2018; 14:577–589
Reality: secondary progression starts much before formal SPMS diagnosis is made

Animal data suggest that SC administration could be important to maintain protective immunity (Marginal Zone B cells)

SC injection enables potent depletion of follicular B cells while maintaining the level of MZ B cells\(^1\)

Sparing of marginal zone B-Cells in the spleen, enables protection against important infections\(^2\)

Animal data suggest that SC administration is important for targeting lymph nodes

Preferential distribution to lymph nodes blocks activation of pathogenic T cells by autoreactive B cells, fighting MS in a critical battlefield

2. Data on File
Subcutaneous injections result in different tissue distribution as compared to intravenous infusions, with potential preservation of host defense, while maintaining high efficacy

**Sub-cutaneous administration**
Lymph nodes are important battlefields in MS, where B cells activate T cells\(^1,2\)

**Intra-venous administration**
The spleen is also rich in CD20+ B-cells\(^7,8\). Marginal Zone CD20+B-cells\(^9\) are very important for protective immunity and thus need to be preserved\(^10\)

---

Primary progressive MS (PPMS) study considerations

- PPMS affects 10-15% of MS population
- Progression independent of inflammation remains poorly understood and unsolved
- Comparing with ocrelizumab and rituximab in PPMS patients would require large number of patients (>2100 patients)
- Placebo-controlled design might pose ethical challenges and operational complexity
**BOLD Study**: Siponimod therapeutic dose was selected in RMS population

Significant efficacy of siponimod on active MRI lesions and relapse rates

*Siponimod 2 mg is the current therapeutically relevant dose for multiple sclerosis.*

**Active MRI Lesions**

![Graph showing active MRI lesions](image_url)

**Annualized Relapse Rate**

![Graph showing annualized relapse rate](image_url)

*Significant efficacy of siponimod on active MRI lesions and relapse rates.*

*Siponimod dose (mg)***

<table>
<thead>
<tr>
<th>Active MRI Lesions</th>
<th>Annualized Relapse Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo 0.25 mg</td>
<td>0.58 (0.34, 1.00)</td>
</tr>
<tr>
<td>0.5 mg</td>
<td>0.55^ (0.32, 0.93)</td>
</tr>
<tr>
<td>1.25 mg</td>
<td>0.61 (0.34, 1.07)</td>
</tr>
<tr>
<td>2 mg</td>
<td>0.23^ (0.08, 0.61)</td>
</tr>
<tr>
<td>10 mg</td>
<td>0.30 (0.15, 0.61)</td>
</tr>
</tbody>
</table>

*^p<0.05 vs. placebo. Siponimod 2 mg is the current therapeutically relevant dose for multiple sclerosis. CUAL, combined unique active lesions, defined as new Gd-enhanced lesions on T1-weighted, or new or enlarging lesions on T2-weighted MRI scans, without double counting; MRI, magnetic resonance imaging; RRMS, relapsing–remitting multiple sclerosis. Selmaj K et al. Lancet Neurol 2013;12:756–67. Cohort 1: 0.5, 2 and 10 mg - treated for 6 months; Cohort 2: 0.25 and 1.25 mg, treatment was initiated after 3 months. So overall treatment duration for Cohort 2 was 3 months only. Siponimod 2 mg is the current therapeutically relevant dose for multiple sclerosis.*

*Siponimod dose (mg)***

<table>
<thead>
<tr>
<th>Siponimod (mg)</th>
<th>N</th>
<th>APR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25 mg</td>
<td>51</td>
<td>0.58 (0.34, 1.00)</td>
</tr>
<tr>
<td>0.5 mg</td>
<td>43</td>
<td>0.55^ (0.32, 0.93)</td>
</tr>
<tr>
<td>1.25 mg</td>
<td>42</td>
<td>0.61 (0.34, 1.07)</td>
</tr>
<tr>
<td>2 mg</td>
<td>49</td>
<td>0.23^ (0.08, 0.61)</td>
</tr>
<tr>
<td>10 mg</td>
<td>50</td>
<td>0.30 (0.15, 0.61)</td>
</tr>
</tbody>
</table>

*Significant efficacy of siponimod on active MRI lesions and relapse rates.*
The realities of SPMS burden significantly impact day-to-day activities and ability to work

“SPMS is the scariest possible news because it has the “least everything”: least information, least hope, least attention, least conversation, least path forward.”

Stacey, progressing patient engaged with local and international MS groups

Physical adaptations can be made in the work environment to sustain employment; however, when you start noticing yourself that you’re just not able to do things the way that you could before, that becomes very, very distressing.

Qualitative interview series with MS healthcare providers

In comparison to RRMS…

- +23% Activity impairment
- +17% Overall work impairment
- +12% Missed time from work
- -20% Employment rate

# Agenda

## Timing | Q&A | Session | Presenters
---|---|---|---
12:00 – 13:00 | | Registration / light lunch | 
13:00 | | Opening | Samir Shah
13:00 – 13:20 | 5 min | Pipeline, platforms | John Tsai
13:20 – 14:20 | 30 min | AveXis AVXS-101 | Dave Lennon, Brian Kaspar
14:20 – 15:15 | 30 min | Oncology Radioligand therapies, ACZ885 in NSCLC, SEG101, BYL719 | Liz Barrett, Samit Hirawat
15:15 – 15:45 | | Break | 
15:45 – 16:45 | 30 min | Upcoming launches (late-stage pipeline) QAW039, RTH258, BAF312, OMB157 | John Tsai, Danny Bar Zohar, Paul Hudson
16:45 – 17:15 | 10 min | Near term value drivers Cosentyx®, Entresto®, Gilenya® | Paul Hudson, John Tsai
17:15 – 17:30 | 15 min | Q&A session | Vas Narasimhan, Harry Kirsch, John Tsai, Paul Hudson, Liz Barrett
17:30 | | Cocktail | All
### Cosentyx® addresses main needs of dermatologists and rheumatologists

<table>
<thead>
<tr>
<th>Dermatologists</th>
<th>Rheumatologists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear or almost clear skin in PsO</td>
<td>PsA</td>
</tr>
<tr>
<td>Addresses other manifestations of psoriatic disease</td>
<td>AS</td>
</tr>
<tr>
<td>Safe and well tolerated</td>
<td>Safe and well tolerated</td>
</tr>
<tr>
<td>Long-term efficacy / safety data (5 years)</td>
<td>Long-term efficacy / safety data (5 years)</td>
</tr>
<tr>
<td>Access</td>
<td>Access</td>
</tr>
</tbody>
</table>

Exploring additional areas of high unmet medical need for patients, potentially expanding Cosentyx® into new indications
Confidence in Cosentyx® comes from 100 studies and extensive Ph3 clinical trial program in PsO, PsA and AS

Source: Novartis, Data on file  
Note: Many of the cited studies are ongoing. Approved indications for secukinumab are moderate-to-severe plaque psoriasis, psoriatic arthritis and ankylosing spondylitis, according to the product label.
Cosentyx® blocks IL-17A, the cornerstone cytokine in PsO, PsA, AS

2/3 of patients have – beyond plaque psoriasis – scalp, nail, palmoplantar and/or joint involvement

Only 34% have plaque psoriasis alone

The ARROW study – to advance our understanding of IL-17 vs IL-23 inhibition

- Designed to show that secukinumab is superior to guselkumab in clearing ustekinumab-resistant skin plaques
- Immune mechanisms responsible for ustekinumab-resistant plaques are shared by other persistent forms of disease, including psoriatic arthritis, ankylosing spondylitis, palmoplantar, nails
- If positive, ARROW will increase evidence of the superior mechanism of Cosentyx® in achieving complete control of psoriatic disease
- Expected read-out: end 2019
The PREVENT study – Cosentyx® in non-radiographic axial spondyloarthritis

A Phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of secukinumab in patients with non-radiographic axial spondyloarthritis

- **Planned enrolment:** 555 patients
- **Population:** NSAID-IR, open for biologic-IR and DMARD-IR
- **Study start date:** April 2016
- **LPFV (enrollment) completion date:** May 2018

Primary efficacy endpoint at Weeks 16 and 52

ASAS40 response rate with secukinumab vs placebo

ASAS40, Assessment of SpondyloArthritis International Society criteria (ASAS) 40% criteria; biologic-IR, biologic inadequate responders; DMARD-IR, disease-modifying anti-rheumatic drug inadequate responders; NSAID-IR, non-steroidal anti-inflammatory drug inadequate responders; Biologic-IR patients are patients who have had an inadequate response to not more than 1 anti-TNF agent; ClinicalTrials.gov (NCT02696031)
Actively exploring expansion beyond the three currently approved indications

**Base (approved Indications)**

- PsO (psoriasis)
- PsA (psoriatic arthritis)
- AS (ankylosing spondylitis)

**Further expansion (ongoing activities)**

- Nr-ax SpA (non-radiographic axial SpA)
- HS (hidradenitis suppurativa)
- Pediatric indications: Juvenile idiopathic arthritis and enthesitis related arthritis

**Other indications & activities (exploration phase)**
Potential additional dermatology indications

- Necrobiosis Lipidica Diabeticorum (NLD)
- Pityriasis Rubra Pilaris (PRP)
- Lichen Planopilaris (LPP)
- Ichthyosis
- Cutaneous Dermatomyositis (CDM)
- Pyoderma Gangrenosum (PG)
- Rosacea
- Vitiligo
- Alopecia Areata (AA)
- Atopic Dermatitis (AD)

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New evidence potentially expands Entresto® to new indications and reinforcing position as foundational treatment in HF

- New data strengthens Entresto® as the new standard of care position in HFrEF, and could transform hospitalizations into a key opportunity for Entresto initiation

- Entresto® has potential to be first approved treatment for HFpEF, based on a positive PARAGON-HF, likely driven by total HF hospitalizations reduction

- Following PARADISE-MI, Entresto® benefits could be further expanded to heart failure prevention in post-AMI patients

1. HF: heart failure. 2. HFrEF: heart failure with reduced ejection fraction. 3. HFpEF: heart failure with preserved ejection fraction. 4. post-AMI: post acute myocardial infarction. Note: HFpEF and post-AMI are future indications under development. Entresto® is not approved to treat these conditions.
PIONEER & TRANSITION complement PARADIGM with data on in-hospital initiation, RAAS\(^1\) naive & de novo patients

Pivotal HFrEF morbidity and mortality study
Entresto\(^\circledR\) vs. enalapril (RCT)

**Ambulatory patients (N=8442)**
- No ACEi/ARB\(^2\) naive or new onset HFrEF\(^3\) patients
- 20% RRR in CV death or HF hospitalization vs. enalapril\(^4\)
- Reductions in NT-proBNP\(^5\) associated with CV death and HF hospitalization benefits for Entresto\(^6\)
- Observed as early as 4 weeks\(^4\)

**Safety and tolerability of Entresto\(^\circledR\) initiation PRE- vs POST-discharge**
Open label Entresto\(^\circledR\)

**Stabilized ADHF\(^7\) patients (N=1002)**
- 24% ACEi/ARB naive
- 29% new onset HFrEF

Initiation of Entresto\(^\circledR\) shortly after stabilization of ADHF\(^7\) is well tolerated, both in-hospital and shortly after discharge\(^8\)

**Efficacy and safety of Entresto\(^\circledR\) initiation PRE-discharge**
Entresto\(^\circledR\) vs. enalapril

**Stabilized ADHF patients (N=736)**
- 52% ACEi/ARB naive
- 34% new onset HFrEF

- Change from baseline in NT-proBNP
- Composite endpoint of serious clinical outcomes (death, HF re-hospitalization, LVAD\(^9\), listed for cardiac transplantation)
- Safety

To be presented at AHA (Nov 11)

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HF hospitalizations could become a key opportunity to further drive Entresto® initiations

US Epidemiology

Total eligible HFrEF² patients

2,450k

Annual hospitalizations

500k

Unique hospitalized patients annually

300k

Key opportunity for Entresto® initiation

- HF hospitalizations are a key trigger for treatment optimization
- Physicians and patients are receptive to treatment change following a HF hospitalization
- HF guidelines² recommend to initiate and uptitrate disease modifying treatment in-hospital

1. HFrEF: heart failure with reduced ejection fraction.  2. ESC and ACC/AHA/HFSA guidelines
**Ph3 expansion studies with potential to make Entresto® the first approved treatment in HFP EF¹ and expand to HF² prevention**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Indication / population</th>
<th>Endpoints</th>
<th>Status</th>
<th>Next expected milestones</th>
<th>US eligible patients (k)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PARAGONHF</strong></td>
<td>HFP EF, LVEF³ &gt;45% N=4822</td>
<td>Novel primary composite endpoint: CV death and total (first &amp; recurrent) HF hospitalization</td>
<td>Fully enrolled; IA⁴ in Aug-2018: study continues as planned</td>
<td>First interpretable results expected Q3 2019 Planned filing in Q4 2019</td>
<td>2,450</td>
</tr>
<tr>
<td><strong>PARALLAXHF</strong></td>
<td>HFP EF, LVEF &gt;40% N=2500</td>
<td>Biomarkers, functional measures, symptoms</td>
<td>Enrolling</td>
<td>Completion expected Q1 2020</td>
<td></td>
</tr>
<tr>
<td><strong>PARADISE-MI</strong></td>
<td>Post-AMI⁵ with evidence of left ventricular dysfunction and/or pulmonary congestion, without prior known history of CHF⁶ N=4650</td>
<td>Composite primary endpoint: CV death, HF hospitalization and outpatient HF</td>
<td>Enrolling</td>
<td>Completion expected Q3 2020</td>
<td>140 p.a.</td>
</tr>
</tbody>
</table>

1. HFP EF: heart failure with preserved ejection fraction.  2. HF: heart failure.  3. LVEF: left ventricular ejection fraction.  4: IA: interim analysis.  5. Post – Acute Myocardial Infarction.  6. Chronic Heart Failure

Note: HFP EF and post-AMI are future indications under development. Entresto® is not approved to treat these conditions.
If approved in HFpEF\(^1\), Entresto\(^\text{®}\) will shape a new disease management paradigm

<table>
<thead>
<tr>
<th>No specific treatments approved for HFpEF</th>
<th>Patient management is focused on treating comorbidities and symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFpEF diagnosis is largely one of exclusion</td>
<td>HF(^2) specific biomarkers may support patient identification</td>
</tr>
<tr>
<td>Particular patient profile</td>
<td>More likely to be older, female, and hypertensive compared to HFrEF(^3) patients</td>
</tr>
<tr>
<td>Higher proportion retained by GPs(^4)</td>
<td>HFpEF patients are more likely to be managed by GPs</td>
</tr>
<tr>
<td>Morbidity and mortality</td>
<td>HFpEF patients face similar hospitalization burden, but notably a lower CV mortality rate(^5) vs. HFrEF</td>
</tr>
</tbody>
</table>

In patients with clinical HF, the prevalence of HFpEF is estimated to be up to 50%\(^6\)

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Note: HFpEF is a future indication under development. Entresto\(^\text{®}\) is not approved to treat this condition.
Entresto®: the new standard of care in HFrEF\(^1\), with potential for growth in new patient segments and indications

- Strong momentum in HFrEF, on track to exceed USD 1bn in 2018
- The only treatment proven superior to ACEi\(^2\) in helping patients to live longer and feel better
- Entresto® standard of care position further supported by new in-hospital use data, with additional data upcoming in HFpEF\(^3\) and Post-AMI\(^4\)

1. HFrEF: heart failure with reduced ejection fraction.  2. ACEi: angiotensin-converting-enzyme inhibitor.  3. HFpEF: heart failure with preserved ejection fraction.  4. post-AMI: post acute myocardial infarction.  Note: pEF and PAMI are future indications under development. Entresto® is not approved to treat these conditions
Gilenya® continues to provide positive data eight years after launch

- >260,000 patients treated worldwide (595,354 PY Exposure)\(^1\)
- >23,000 patients exposed to fingolimod in clinical trials so far\(^2\)

<table>
<thead>
<tr>
<th>TRANSFORMS</th>
<th>ASSESS</th>
<th>PARADIGMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head-to-head trial</td>
<td>Head-to-head trial</td>
<td>Head-to-head trial</td>
</tr>
<tr>
<td>(vs. Avonex®) data</td>
<td>(vs. Copaxone®) data</td>
<td>(vs. Avonex®) data</td>
</tr>
<tr>
<td>in Adult RMS</td>
<td>in Adult RMS</td>
<td>in pediatric RMS</td>
</tr>
</tbody>
</table>

2. Novartis data on file

Avonex® is a registered trademark of Biogen. Copaxone® is a registered trademark of Teva Pharmaceuticals LTD
Gilenya® first and only DMT to show efficacy in a randomized, controlled pediatric MS trial

PARADIGMS study showed:
- 82% lower relapse rate
- significant reductions in MRI lesions
- significantly less brain shrinkage
- safety profile comparable to previous Gilenya® clinical trials

FDA approved Gilenya in May 2018 for pediatric MS patients

Positive CHMP opinion received, EMA approval expected by end of November

Gilenya® 0.5mg is first DMT to show superior efficacy in RMS vs. Copaxone® in a head to head trial1,2

Aggregate ARR up to Month 12

- Gilena® 0.5mg - significant 40.7% relative reduction in ARR vs. Copaxone®
- Gilena® 0.25mg - achieved numerical risk reduction (NS) in ARR vs. Copaxone®
- Safety consistent with the known fingolimod profile
- Copaxone® arm had more discontinuations due to AE and unsatisfactory treatment effects as compared to Gilena®

ARR - Annualized relapse rate  AE - Adverse events  NS - Not statistically significant  1. Post-approval commitment to FDA; randomized, controlled Ph4 study; 1,064 patients  2. A formal comparison of fingolimod 0.5mg vs. 0.25mg was not planned (study was not powered for such a comparison)  Copaxone® is a registered trademark of Teva Pharmaceuticals LTD
Back-up
**Cosentyx® PREVENT study – what is different?**

| IL17A | First new, promising MoA investigated after TNF-alpha studies  
No approved/reimbursed biologic for nr-axSpA in many countries, e.g., US, TNF-IR in EU |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zero progression? 1st interventional study to investigate effects on structural progression on x-ray and MRI in nr-axSpA</td>
</tr>
<tr>
<td></td>
<td>Investigates natural disease course by innovative, flexible, up to 1-year placebo control group</td>
</tr>
<tr>
<td>Regulatory agencies</td>
<td>Potential to be the 1st Approved anti-IL-17 treatment for nr-axSpA</td>
</tr>
<tr>
<td>✔️</td>
<td>Central x-ray and MRI reading for inclusion guarantees clean nr-axSpA study population; no dilution by mechanical back pain pts</td>
</tr>
<tr>
<td>✗</td>
<td>A unique opportunity for trial patients to receive optimal medical care and clarity around diagnosis, avoidance of overtreatment due to close monitoring by experts, and the ability to help other nr-axSpA patients by advancing scientific knowledge</td>
</tr>
</tbody>
</table>
**NT-pro-BNP lowering with Entresto® reliably associated with reduced CV death and HF hospitalizations**

- NT-pro-BNP is a guideline-recommend diagnostic and prognostic biomarker for HF; marker of cardiac ventricular wall stress

- In PARADIGM, Entresto® was twice as likely to cause a meaningful reduction in NT-proBNP, compared to enalapril
  - Changes observed as early as week 4 and associated with improved CV outcomes

- Entresto® effects on NT-pro-BNP early after stabilization for an acute decompensated HF event from TRANSITION and PIONEER to be presented at AHA

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ASSESS study background and design

- ASSESS study\(^1\) was part of the post-approval commitment to FDA in 2010; rationale was to identify the minimally effective dose of fingolimod in RMS

- Agreement was to conduct a randomized controlled study assessing fingolimod 0.5 mg and 0.25 mg vs. Copaxone® 20mg/d
  - Each fingolimod dose was to be tested separately vs. Copaxone® (Primary endpoint – relapse rate)

- The study was initially designed to recruit 2,550 RRMS patients; In agreement with FDA, sample size was reduced to 1064 patients given the challenges in recruitment, therefore reducing the power to detect smaller effects sizes.

<table>
<thead>
<tr>
<th>Screening</th>
<th>Dose-blind treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>month -1 to Day 0</td>
<td>12 months</td>
<td></td>
</tr>
<tr>
<td>Randomisation</td>
<td>1:1</td>
<td></td>
</tr>
<tr>
<td>Month 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 6</td>
<td><strong>Fingolimod 0.5 mg / day</strong>*</td>
<td></td>
</tr>
<tr>
<td>Month 9</td>
<td><strong>Fingolimod 0.25 mg / day</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Glatiramer acetate 20 mg / day s.c.</strong></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End of treatment</td>
<td>Follow-up visit</td>
<td></td>
</tr>
<tr>
<td>Month 12</td>
<td>Month 15</td>
<td></td>
</tr>
<tr>
<td>MRI visit</td>
<td></td>
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</tbody>
</table>

Copaxone® is a registered trademark of Teva Pharmaceuticals LTD 1. Novartis data on file
Key definitions and trademarks

This presentation contains several important words or phrases that we define as below:

AE: Adverse Event
ALL: Acute lymphatic leukemia
AMD: Age-Related Macular Degeneration
AML: Acute myeloid leukemia
Approval: In Pharmaceuticals and Alcon in US and EU; each indication and regulator combination counts as approval; excludes label updates, CHMP opinions alone and minor approvals
aRCC: advanced renal cell cancer
AS: Ankylosing Spondylitis
bid: twice a day
BC: Breast cancer
BCMA: B-cell maturation antigen
BCVA: best corrected visual acuity
BS: Biosimilars
BTD: Breakthrough therapy designation
CGRP: Calcitonin gene-related peptide
CLL: Chronic lymphocytic leukemia
CM: Chronic migraine
CML: Chronic myeloid leukemia
COPD: Chronic Obstructive Pulmonary Disease
CR: complete remission
CRC: Colorectal Cancer
CSU / CIU: Chronic spontaneous urticaria / Chronic idiopathic urticaria
CVRR: Cardiovascular risk reduction
DLBCL: Diffuse large B-cell lymphoma
DMC: Data monitoring committee
EF: ejection fraction
EM: Episodic migraine
FL: Follicular lymphoma
FPFV: First patient first visit
GBM: Glioblastoma multiforme
HF: Heart failure
HFpEF: Heart failure with preserved ejection fraction
HFrEF: Heart failure with reduced ejection fraction
HR+/HER2- mBC: Hormone Receptor positive / Human Epidermal growth factor receptor 2 negative metastatic breast cancer
LoE: Loss of exclusivity
M/M: Multiple myeloma
MF: Myelofibrosis
MI: Myocardial infarction
MS: Multiple sclerosis
NASH: Non-Alcoholic Steatohepatitis
NET: Neuroendocrine tumor
NSCLC: Non-small cell lung cancer
NTD: New Therapeutic Drug
od: once a day
ORR: Overall response rate
OS: Overall survival
PA: Prior authorization
PASi 90: 90% reduction in Psoriasis Area Severity Index from baseline
PFS: Progression free survival
PSA: Prostate specific antigen
PsA: Psoriatic arthritis
PsO: Psoriasis
PV: Polycythemia vera
PY: Prior year
QoL: Quality of Life
RCC: Renal cell cancer
RoP: Retinopathy of prematurity
r/r ALL: relapsed/refractory acute lymphoblastic leukemia
RRMS: relapsing-remitting multiple sclerosis
SCPC: Sickle cell pain crisis
SpA: Spondyloarthropathy
SPMS: Secondary progressive multiple sclerosis
TFR: Treatment-free Remission
TNBC: Triple negative breast cancer
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