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Novartis announced October 30, 2017, that it had entered a memorandum of understanding with Advanced Accelerator Applications (AAA) under which Novartis intends to commence a tender offer for 100% of the share capital of AAA. The transaction is subject to certain closing conditions. Novartis will commence a tender offer upon completion of works council consultation and AAA's Board of Directors recommending the tender offer to AAA shareholders. The senior management and Directors of AAA have, in their capacity as shareholders of AAA, undertaken to tender their shares into the proposed tender offer. The transaction is additionally subject to (i) the valid tender pursuant to the tender offer of ordinary shares (including ordinary shares in the form of American Depositary Shares) of AAA representing at least 80% of the outstanding ordinary shares on a fully diluted basis and (ii) receipt of customary transactional regulatory approvals and other customary closing conditions. Until such time as the closing conditions are satisfied, Lutathera® remains under the custody and control of AAA. Novartis does not currently own or control these projects and will not have the ability to influence them until closing of the proposed acquisition of AAA which is subject to certain closing conditions and regulatory approvals within H1 2018.
<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>13:30 – 14:00</td>
<td>Registration</td>
</tr>
<tr>
<td>14:00 – 14:30</td>
<td>Introduction</td>
</tr>
<tr>
<td>14:30 – 15:15</td>
<td>RTH258</td>
</tr>
<tr>
<td>15:15 – 15:45</td>
<td>AMG 334</td>
</tr>
<tr>
<td>15:45 – 16:15</td>
<td>Break</td>
</tr>
<tr>
<td>16:15 – 17:00</td>
<td>Cosentyx®</td>
</tr>
<tr>
<td>17:00 – 17:30</td>
<td>ACZ885</td>
</tr>
<tr>
<td>17:30 – 18:00</td>
<td>Q&amp;A session</td>
</tr>
<tr>
<td>18:00</td>
<td>Cocktail with management</td>
</tr>
</tbody>
</table>
Continued strong track record of R&D excellence

- #1 In US/EU approvals past 10 years
- #3 In pipeline replacement power
- 18 Breakthrough Therapy Designations
- 175+ Projects in the clinic
- 90+ New molecular entities in the clinic
- 500+ Active clinical trials

1. Data for Global Drug Development: Innovative Medicines and Sandoz biosimilars
2. In number of new molecular entities (NMEs) approved including fixed dose combinations 2007-2016
3. Source: Novartis peer group analysis based on data from Evaluate Pharma (download from January 16, 2017) as presented during Novartis R&D day January 2017
4. Since introduction of Breakthrough Designation (BTD) by the FDA, the Novartis pipeline included a total of 18 BTDs of which 15 are currently actively under development or in approved indications
R&D priorities to lead the industry in innovation into the future

Continuously strengthening the portfolio of therapies

Addressing the major unmet needs of today

Focusing on transformational platforms

Building an industry-leading intelligent, agile organization

Digitally enabled productivity

Next-gen platform for data science
Full pipeline of late stage assets – key expected launches in Innovative Medicines Division

1. Exact launches and timing depends on filing date, HAs decisions and timelines.

*Advanced Accelerator Applications (AAA) pipeline project. Novartis does not currently own or control this project and will not have the ability to influence it until closing of the proposed acquisition of AAA, which is subject to certain closing conditions and regulatory approvals within H1 2018.
JULIET study in DLBCL shows strong Duration of Response
74% of responders were relapse-free at 6 months

r/r DLBCL responses to therapy

<table>
<thead>
<tr>
<th>Response</th>
<th>n</th>
<th>ORR</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best overall response</td>
<td>81</td>
<td>53%</td>
<td>40%</td>
</tr>
<tr>
<td>Month 3 response</td>
<td>81</td>
<td>38%</td>
<td>32%</td>
</tr>
<tr>
<td>Month 6 response</td>
<td>46</td>
<td>37%</td>
<td>30%</td>
</tr>
</tbody>
</table>

- 6-month probability of being relapse-free was 74%
- Median DOR and OS not reached
- 6-month probability of overall survival was 64.5%
- No patient who achieved a response (CR or PR) proceeded to allogenic- or auto-SCT

ASH December 9-12, 2017 Paper 577 Primary Analysis of Juliet: A Global, Pivotal, Phase 2 Trial of CTL019 in Adult Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma

ORR - overall response rate, CR - complete response, DOR - duration of response, OS - overall survival, SCT - stem cell transplant
Kymriah™ approval and submissions

Pediatric and young adult relapsed/refractory ALL
• First ever approval for a CAR-T cell therapy received

r/r DLBCL
• Submitted in October 2017

Pediatric and young adult relapsed/refractory ALL
• Submitted in November 2017

r/r DLBCL
• Submitted in November 2017

Novartis has successfully demonstrated a 22-day turnaround time for manufacturing Kymriah™ in the commercial setting

Kymriah™ was developed in collaboration with the University of Pennsylvania
# Novartis CAR-T franchise overview

<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 ALL¹</td>
<td></td>
<td></td>
<td></td>
<td>EU</td>
<td>US</td>
</tr>
<tr>
<td>CD19 CAR-T</td>
<td>r/r DLBCL²</td>
<td></td>
<td></td>
<td></td>
<td>US/EU</td>
<td></td>
</tr>
<tr>
<td>CD19 CAR-T</td>
<td>DLBCL in 1st relapse²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD19 CAR-T</td>
<td>r/r FL³</td>
<td>Starting 2018</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD19 CAR-T</td>
<td>r/r DLBCL² in combination with pembrolizumab</td>
<td>Starting 2018</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD19 CAR-T</td>
<td>CLL⁴</td>
<td></td>
<td></td>
<td>Starting 2018</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAR-T-BCMA</td>
<td>r/r Multiple Myeloma</td>
<td></td>
<td></td>
<td>Starting 2018</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAR-T-EGFRvIII</td>
<td>Recurrent GBM⁵</td>
<td></td>
<td></td>
<td>Started</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAR-T-Meso</td>
<td>Advanced ovarian cancer, Mesothelioma</td>
<td></td>
<td></td>
<td>Started</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. ALL – acute lymphoblastic leukemia  
2. DLBCL – diffuse large B-cell lymphoma  
3. FL – follicular lymphoma  
4. CLL – chronic lymphocytic leukemia  
5. GBM – glioblastoma multiforme
SEG101 (crizanlizumab) – planned filing in 2018

- Sickle cell disease prevalence 100,000 in US/EU\(^1\), leading cause of hospitalization
- US submission planned for Q4 2018
- EU submission planned for Q1 2019
- Phase 2 PK/PD study with long-term efficacy and safety in adult patients with sickle cell disease is ongoing
- Phase 2 PK/PD study with long-term efficacy and safety in pediatric patients is planned to start in Q2 2018


Overview of $^{177}$Lu-DOTATATE (Lutathera®)

- 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.

- $^{177}$Lu-DOTATATE is composed of a lutetium radionuclide chelated to a peptide. Lutetium emits mostly high energy electrons ($\beta$-particles; half-life 6.6 days).

- The peptide is designed to target somatostatin receptors with high binding affinity.

Source: graphics with kind permission of Advanced Accelerator Applications for this presentation only

1. Lutathera® is a registered trademark of Advanced Accelerator Applications

Novartis does not currently own or control these projects and will not have the ability to influence them until closing of the proposed acquisition of AAA which is subject to certain closing conditions and regulatory approvals within H1 2018.
Lutathera® is the first-in-class RLT with paradigm-changing efficacy for the treatment of unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in adults

- 79% risk reduction of progression or death (P<.001) vs high-dose octreotide LAR (60 mg)
- Median PFS: not reached vs 8.4 months


Novartis does not currently own or control these projects and will not have the ability to influence them until closing of the proposed acquisition of AAA which is subject to certain closing conditions and regulatory approvals within H1 2018
Expected outlook for Advanced Accelerator Applications

- $^{177}$Lu-Dotatate FDA PDUFA date January 26, 2018
- $^{177}$Lu-PSMA-R2 entering Phase 1/2 for prostate cancer
- Additional solid tumor types to be explored with $^{177}$Lu-based radioligand therapy and $^{68}$Ga-based companion diagnostics

Novartis does not currently own or control these projects and will not have the ability to influence them until closing of the proposed acquisition of AAA which is subject to certain closing conditions and regulatory approvals within H1 2018.
BAF312 efficacy in SPMS creates opportunity to address an unmet need in more advanced patients

MS disease spectrum

<table>
<thead>
<tr>
<th></th>
<th>CIS</th>
<th>RRMS</th>
<th>rSPMS</th>
<th>nrSPMS</th>
<th>PPMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse frequency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Diagnosed patient pool (US+EU5)

- 90K
- 560K
- 120K
- 120K
- 102K

BAF312 demonstrates high efficacy in MRI measures of disease progression

- In EXPAND, 21% and 26% reduction of 3m and 6m confirmed disability progression

- Consistent effects on MRI measures of disease progression:
  - T2 lesion volume
    - 75% and 83% reduction
  - Brain volume loss: per-protocol analysis
    - 48% and 31% reduction

1. p=0.013, p=0.006 for 3- and 6-month confirmed disability progression
2. 48% reduction at 0-12 months (p<0.0001), 31% reduction at 0-24 months (p<0.0001)

PARADIGMS: Gilenya® was superior to interferon β-1a in pediatric patients with multiple sclerosis

- First successfully completed Ph3 trial for pediatric patients
  - 82% lower relapse rate
  - significant reductions in MRI lesions
  - significantly less brain shrinkage
  - safety profile comparable to previous Gilenya® clinical trials

- Possible extension of regulatory data protection by 1 year in EU to March 2022

OMB157 (ofatumumab) on track for 2019 filing in RRMS

OMB157 suppressed >90% of new MS lesions in the brain as measured by MRI\(^1\)

- Two parallel Ph3 studies vs. oral teriflunomide in relapsing MS on track to complete enrollment in early 2018
- Planned filing 2019

\(^1\) Sorensen PS et al., Neurology 2014;82(7):573-81; MRI = Magnetic Resonance Imaging; pooled analysis of all doses levels in the Sorensen study (Ph 2a); 100 mg, 300 mg, 700 mg - i.v.
## Entresto® HFpEF expansion studies on track

<table>
<thead>
<tr>
<th>Trial</th>
<th>Indication / population</th>
<th>Endpoints</th>
<th>Status</th>
<th>Next expected milestone</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARAGON HF</td>
<td>HF-pEF¹</td>
<td>Novel primary composite endpoint: CV death and total (first &amp; recurrent) HF hospitalization</td>
<td>Fully enrolled 4 months ahead of plan</td>
<td>Interim analysis H2 2018 Filing in 2019</td>
</tr>
<tr>
<td>PARALLAX HF</td>
<td>HF-pEF¹</td>
<td>Biomarkers, symptoms and functional measures</td>
<td>Enrolling</td>
<td>Completion 2020</td>
</tr>
</tbody>
</table>

Transition study on pre- vs. post-discharge following ADHF² (HF-rEF³) expected to complete 2018
PioneerHF study in hospital initiation vs. enalapril following ADHF expected to complete 2018
Paradise-MI study in Post-AMI expected to complete 2019

1. HF-pEF- heart failure with preserved ejection fraction  
2. ADHF - acute decompensated heart failure  
3. HF-rEF- heart failure with reduced ejection fraction

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Developing leading portfolio in moderate to severe asthma

Moderate/severe asthma portfolio

QVM149\(^1\): inhaled combination therapy
- Once-daily triple combination for Ex-US
- Pivotal Ph3 trials ongoing; planned filing 2019

QAW039: potential first-in-class oral treatment for severe asthma
- CRTh2 antagonist; add-on to ICS/LABA or ICS/LABA/LAMA\(^2\)
- Pivotal Ph3 trials ongoing; planned filing 2019

Xolair®: first choice biologic for allergic asthma
- Xolair® with US\(^3\) approval for pediatric moderate to severe persistent allergic asthma

CSJ117: inhaled anti-TSLP\(^4\) antibody fragment
- Advancing into Ph2 studies

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1. Fixed-dose combination of indacaterol, glycopyrronium and mometasone
2. LABA = long-acting β2-agonist; ICS = inhaled corticosteroid; LAMA = long-acting muscarinic antagonist
3. Novartis co-promotes Xolair® with Genentech in the US and shares a portion of operating income, but we do not record any US sales. Novartis records all sales of Xolair® outside the US
4. Thymic Stromal LymphoPoetin cytokine
# Progressing late stage development of potential blockbusters

<table>
<thead>
<tr>
<th>Therapeutic area</th>
<th>Molecule</th>
<th>Indication</th>
<th>MoA</th>
<th>Exp. pivotal trial readout</th>
<th>Current status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncology</td>
<td>Kisqali® (ribociclib)</td>
<td>HR+/HER2- advanced or metastatic breast cancer</td>
<td>CDK4/6 inhibitor</td>
<td>✓</td>
<td>Approved in US and EU</td>
</tr>
<tr>
<td></td>
<td>Kymriah™ (CAR-T)</td>
<td>r/r B-Cell ALL, r/r DLBCL</td>
<td>CAR-T</td>
<td>✓²</td>
<td>Approved in US, filed in EU for ped. and young adult r/r ALL, filed in US and EU for DLBCL</td>
</tr>
<tr>
<td></td>
<td>SEG101 (erianitumab)</td>
<td>Sickle cell pain crises</td>
<td>Anti-P-selectin</td>
<td>✓³</td>
<td>On track for submission in 2018</td>
</tr>
<tr>
<td>Cardio-metabolic</td>
<td>LCZ696 (Entresto®)</td>
<td>Heart failure with preserved EF</td>
<td>ARNI</td>
<td>2019</td>
<td>On track</td>
</tr>
<tr>
<td></td>
<td>ACZ885 (canakinumab)</td>
<td>CV risk reduction</td>
<td>Anti-IL1β</td>
<td>✓</td>
<td>Positive pivotal trial read out</td>
</tr>
<tr>
<td>Neuroscience</td>
<td>OMB157 (olatumumab)</td>
<td>Relapsing multiple sclerosis</td>
<td>CD20</td>
<td>2019</td>
<td>On track</td>
</tr>
<tr>
<td></td>
<td>BAF312 (siponimod)</td>
<td>Secondary progressive multiple sclerosis</td>
<td>S1P receptor modulator</td>
<td>✓</td>
<td>Path forward agreed with FDA</td>
</tr>
<tr>
<td></td>
<td>AMG 334 (erenumab)</td>
<td>Prophylaxis of migraine</td>
<td>CGRP receptor antagonist</td>
<td>✓</td>
<td>Filed in US and EU</td>
</tr>
<tr>
<td>Immunology &amp; Dermatology</td>
<td>AIN457 (Cosentyx®)</td>
<td>Non-radiographic axial SpA</td>
<td>Anti-IL17A</td>
<td>2019</td>
<td>On track</td>
</tr>
<tr>
<td>Respiratory</td>
<td>QVM149 (indacaterol, glycopyrronium, mometasone)</td>
<td>Asthma</td>
<td>LABA + LAMA + ICS</td>
<td>2019</td>
<td>On track</td>
</tr>
<tr>
<td></td>
<td>QAW039 (teviprapt)</td>
<td>Asthma</td>
<td>CRTh2 antagonist</td>
<td>2019</td>
<td>On track</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>RTH258 (brolucizumab)</td>
<td>Neovascular AMD</td>
<td>Anti-VEGF (scFv)</td>
<td>✓</td>
<td>Positive pivotal read out</td>
</tr>
<tr>
<td>Biosimilars</td>
<td>Multiple</td>
<td>Multiple</td>
<td>Multiple</td>
<td>Ongoing</td>
<td>Several approved</td>
</tr>
</tbody>
</table>

1. Blockbuster potential refers to specified indication
2. Breakthrough Therapy designation granted for DLBCL
3. Refers to Ph2 readout; supportive PK study ongoing
4. Based on the unique SPMS population studied in EXPAND, the exact indication language will be a matter of review
5. In collaboration with Amgen; Novartis has AMG 334 rights outside of Japan and co-commercialization in the US
Appendix
Selected key assets in Oncology

- **Kisqali®**: BC
  - CDK4/6 inhibitor
  - MONALEESA-7 in advanced BC with positive readout, MONALEESA-3 and adjuvant study ongoing
  - CAR-T
- **Kymriah™**: B-cell malignancies
  - r/r DLBCL filed, trials in other B-cell malignancies to be started in 2018
  - Anti-P-Selectin
  - Filing planned in 2018
  - BRAF V600 kinase inhibitor + MEK1/2 inhibitor
  - Filing planned in 2017
  - Anti-IL1β
  - Phase 3 studies to start in 2018
- **ACZ885**: NSCLC
  - Phase 3 for PDR001 in melanoma

- **INC280 NSCLC**: 18 IO assets
  - cMET inhibitor
  - Filing planned in 2018
- **BYL719 + fulv BC**: Multiple
  - PI3k inhibitor
  - Filing planned in 2018
- **ABL001 CML**: 18 IO assets
  - Allosteric BCR-ABL Inhibitor
  - Phase 3
- **Jakavi® Acute/Chronic GVHD**: Multiple
  - JAK1/2 inhibitor
  - Phase 3

Kymriah™ was developed in collaboration with the University of Pennsylvania
Selected key assets in Cardio-metabolic

**ACZ885**
- CVRR
- Anti-IL1β
- Filing planned in 2017

**Entresto®**
- Heart failure
- Post-MI, acute MI
- ARNI
- Ph 3 programs reading out 2019-2020

**Apo(a)-LRx**
- High risk CVRR
- Lipoprotein(a) inhibitor
- Phase 2b

**ApoCIII-LRx**
- High risk CVRR
- Apolipoprotein-CIII inhibitor
- Phase 2b initiating

**MAA868**
- Stroke prevention
- Anti-thrombotic
- Preparing Phase 2

**LHW090**
- Resistant hypertension
- NEP inhibitor
- Phase 2

**LIK066**
- Weight loss
- SGLT1/2 inhibitor
- Phase 2

*Note: subject to Akcea Therapeutics option and collaboration agreement*
## Selected key assets in Neuroscience

<table>
<thead>
<tr>
<th>Asset</th>
<th>Disease Area</th>
<th>Stage</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gilenya®</strong>&lt;br&gt;Pediatric MS</td>
<td>Neuropathic pain</td>
<td>Phase 2</td>
<td>S1P receptor modulator, Pediatric MS positive readout</td>
</tr>
<tr>
<td><strong>BAF312</strong>&lt;br&gt;Secondary progressive MS</td>
<td>Sarcopenia, hip fracture</td>
<td>Phase 2</td>
<td>S1P receptor modulator, In filing preparation</td>
</tr>
<tr>
<td><strong>AMG 334</strong>&lt;br&gt;Migraine</td>
<td>Migraine</td>
<td>In filing preparation</td>
<td>CGRP receptor antagonist, Filed with FDA and EMA</td>
</tr>
<tr>
<td><strong>OMB157</strong>&lt;br&gt;Relapsing MS</td>
<td>Sarcopenia, hip fracture</td>
<td>Phase 2</td>
<td>Anti-CD20, Phase 3 readout in 2019</td>
</tr>
<tr>
<td><strong>CNP520</strong>&lt;br&gt;Alzheimer's</td>
<td>Alzheimer's</td>
<td>Phase 2</td>
<td>BACE inhibitor, Phase 2b ongoing</td>
</tr>
<tr>
<td><strong>BYM338</strong>&lt;br&gt;Sarcopenia, hip fracture</td>
<td>Sarcopenia, hip fracture</td>
<td>Phase 2</td>
<td>Activin type-2 receptor mAb, Phase 2</td>
</tr>
<tr>
<td><strong>EMA401</strong>&lt;br&gt;Neuropathic pain</td>
<td>Neuropathic pain</td>
<td>Phase 2</td>
<td>Angiotensin II Type-2 Receptor antagonist, Phase 2</td>
</tr>
</tbody>
</table>

*Novartis R&D and investor day | November 13, 2017*
Selected key assets in Immunology & Dermatology

**Cosentyx®**
PsO, AS, PsA, nrAxSpA
- Anti-IL17
- Phase 3 programs ongoing

**LJN452**
NASH
- FXR agonist
- Phase 2

**VAY785**
NASH
- Pan-caspase inhibitor
- Phase 2

**QGE031**
Chronic spontaneous urticaria
- Anti-IgE
- Phase 2

**ZPL389**
Atopic dermatitis
- H4 receptor antagonist
- Phase 2 to start in 2018

**VAY736**
Primary Sjogren’s syndrome
Autoimmune hepatitis
- Anti-BAFF-R
- Phase 2
## Selected key assets in Respiratory

<p>| | | | |</p>
<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
</table>
|**QAW039**<br>Asthma | • Oral CRTh2 antagonist  
  • Ph3 programs ongoing, expected readouts 2019 |
|**QVM149**<br>Asthma | • LABA+LAMA+ICS  
  • Phase 3, planned filing 2019 |
|**QMF149**<br>Asthma | • LABA+LAMA+ICS  
  • Phase 3, planned filing 2019 |
|**QBW251**<br>Cystic fibrosis | • CFTR potentiator  
  • Phase 2 |
|**ACZ885**<br>Sarcoidosis | • Anti-IL1β  
  • Phase 2 |
|**CSJ117**<br>Asthma | • Inhaled anti-Thymic Stromal LymphoPoetin cytokine antibody fragment  
  • Preparing Phase 2 |
Selected key assets in Ophthalmology

- **RTH258 nAMD**
  - Anti-VEGF
  - Positive pivotal trial read out, planned filing 2018

- **UNR844 Presbyopia**
  - Prodrug to metabolize DHLA
  - Phase 2

- **ECF843 Dry eye**
  - Lubricin
  - Phase 2 starting in 2019
### Pipeline of key projects in confirmatory development

#### Early Clinical Trials

<table>
<thead>
<tr>
<th>Project</th>
<th>Indication</th>
</tr>
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<tbody>
<tr>
<td>ABL001</td>
<td>Malaria</td>
</tr>
<tr>
<td>ABL001</td>
<td>Malaria</td>
</tr>
<tr>
<td>LHW090</td>
<td>Diabetes</td>
</tr>
<tr>
<td>VAY736</td>
<td>Diabetes</td>
</tr>
<tr>
<td>CAD106</td>
<td>Alzheimer’s disease</td>
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<tr>
<td>CAD106</td>
<td>Alzheimer’s disease</td>
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<td>CNP520</td>
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<td>ECF843</td>
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<td>EMA401</td>
<td>Peripheral neuropathy</td>
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<td>INCB060101</td>
<td>Malaria</td>
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<td>QBG251</td>
<td>COPD</td>
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#### Registration Trials – Phase III / Pivotal

<table>
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<tr>
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<tbody>
<tr>
<td>BAF312</td>
<td>Diabetes</td>
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<tr>
<td>BYL719</td>
<td>Diabetes</td>
</tr>
<tr>
<td>VAY785p</td>
<td>Diabetes</td>
</tr>
<tr>
<td>PDR001</td>
<td>Diabetes</td>
</tr>
<tr>
<td>ZPL389</td>
<td>Diabetes</td>
</tr>
<tr>
<td>QAW039</td>
<td>Diabetes</td>
</tr>
<tr>
<td>RTH258</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Kymriah™</td>
<td>Follicular lymphoma</td>
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<td>Kymriah™</td>
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<td>Diabetes</td>
</tr>
<tr>
<td>ACZ885</td>
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</tr>
<tr>
<td>ACZ885</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Arzerra®</td>
<td>Refractory</td>
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<tr>
<td>Cosentyx®</td>
<td>Refractory</td>
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#### In Registration

<table>
<thead>
<tr>
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<th>Indication</th>
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</thead>
<tbody>
<tr>
<td>Lucentis®</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Entresto</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Entresto</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Promacta®/Revolade®</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Signifor®</td>
<td>Diabetes</td>
</tr>
</tbody>
</table>

#### Combination abbreviations:

- fulv: fulvestrant
- NSAI: Non-steroidal aromatase inhibitor
- ltx: letrozole
- tam: tamoxifen
- gsn: goserelin
- Mek: Mekinist®
- tram: trametinib
- dabra: dabrafenib

#### New formulations

- New molecule
- New indication
- New formulation
- Biosimilars

---

27 | Novartis R&D and investor day | November 13, 2017
## Planned filings 2017 to > 2021

<table>
<thead>
<tr>
<th>2017</th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
<th>&gt; 2021</th>
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<tr>
<td><strong>Kymriah™</strong>&lt;sup&gt;a&lt;/sup&gt; Pediatric/young adult acute lymphoblastic leukemia</td>
<td><strong>Tafinlar® + Mekinist®</strong> BRAF V600+ melanoma (adjuvant) &lt;sup&gt;b&lt;/sup&gt;</td>
<td><strong>BAF312</strong>&lt;sup&gt;c&lt;/sup&gt; SPM3&lt;sup&gt;d&lt;/sup&gt;</td>
<td><strong>PDR001 + Taf/Mek</strong> Metastatic BRAF V600+ melanoma</td>
<td><strong>ABL001</strong>&lt;sup&gt;e&lt;/sup&gt; CML 3rd line</td>
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<tr>
<td><strong>ACZ885</strong> Sec. prev. CV events&lt;sup&gt;c&lt;/sup&gt;</td>
<td><strong>BYL719 + fulv HR+, HER2+ postmenopausal adv. BC 2nd line</strong></td>
<td><strong>QAW039</strong> Asthma</td>
<td><strong>QGE031</strong> CAS/C40&lt;sup&gt;f&lt;/sup&gt;</td>
<td><strong>QGE000</strong> CAS/C40&lt;sup&gt;f&lt;/sup&gt;</td>
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<td><strong>Kymriah™ f</strong>&lt;sup&gt;g&lt;/sup&gt; <strong>DBL®&lt;sup&gt;l&lt;/sup&gt;</strong> Pediatric multiple sclerosis</td>
<td><strong>INCB280 NSCLC&lt;sup&gt;c&lt;/sup&gt;</strong></td>
<td><strong>Arzerra&lt;sup&gt;®&lt;/sup&gt; NHL (refractory)</strong></td>
<td><strong>Entresto® Post-acute myocardial infarction</strong></td>
<td><strong>BYM338</strong> Hip fracture recovery</td>
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<td><strong>FTY720</strong> Pediatric multiple sclerosis</td>
<td><strong>LC699&lt;sup&gt;c&lt;/sup&gt;</strong> Cushing’s disease</td>
<td><strong>Cosentyx®&lt;sup&gt;®&lt;/sup&gt;</strong> nrAxiSpA&lt;sup&gt;d&lt;/sup&gt;</td>
<td><strong>Cosentyx® Pts HxH&lt;sup&gt;c&lt;/sup&gt;</strong></td>
<td><strong>VA0736</strong> Autoimmune Hepatitis</td>
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<tr>
<td><strong>LA-EP2006 (pegfilgrastim, US)</strong> Chemotherapy-induced neutropenia and others (same as originator)</td>
<td><strong>RTH258 nAMD&lt;sup&gt;d&lt;/sup&gt;</strong></td>
<td><strong>Entresto® Heart failure (PEF)&lt;sup&gt;c&lt;/sup&gt;</strong></td>
<td><strong>Jakavi® Chronic GVHD&lt;sup&gt;®&lt;/sup&gt;</strong></td>
<td><strong>VA0736</strong> Primary Sjogren’s syndrome</td>
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<tr>
<td></td>
<td><strong>SEG101&lt;sup&gt;c&lt;/sup&gt;</strong> Sickle cell disease</td>
<td><strong>OMB157 Relapsing multiple sclerosis</strong></td>
<td><strong>Jakavi® Chronic GVHD&lt;sup&gt;®&lt;/sup&gt;</strong></td>
<td><strong>VA0785&lt;sup&gt;e&lt;/sup&gt;</strong> NASH&lt;sup&gt;e&lt;/sup&gt;</td>
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<td><strong>LAM320&lt;sup&gt;c&lt;/sup&gt;</strong> MDR&lt;sup&gt;c&lt;/sup&gt; tuberculosis</td>
<td><strong>PDR001&lt;sup&gt;e&lt;/sup&gt; NET&lt;sup&gt;c&lt;/sup&gt;</strong></td>
<td><strong>RTH258 Diabetic macular edema</strong></td>
<td><strong>ECF843&lt;sup&gt;d&lt;/sup&gt;</strong> Dry eye</td>
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<td></td>
<td><strong>Kisqali® + fulv HR+, HGB&lt;sup&gt;c&lt;/sup&gt; postmenopausal adv. BC 1st/2nd line</strong></td>
<td><strong>OMF149&lt;sup&gt;c&lt;/sup&gt;</strong> Asthma</td>
<td><strong>Kymriah™&lt;sup&gt;®&lt;/sup&gt;</strong> ir Follicular Lymphoma</td>
<td><strong>EMA401</strong> Peripheral neuropathy pain</td>
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<tr>
<td></td>
<td><strong>Kisqali®&lt;sup&gt;e&lt;/sup&gt;</strong> ir, groN&lt;sup&gt;d&lt;/sup&gt;, NSAI&lt;sup&gt;d&lt;/sup&gt; groR&lt;sup&gt;d&lt;/sup&gt;, NSAI&lt;sup&gt;d&lt;/sup&gt; groR&lt;sup&gt;d&lt;/sup&gt;</td>
<td><strong>QVM149&lt;sup&gt;c&lt;/sup&gt;</strong> Asthma</td>
<td><strong>Kymriah™&lt;sup&gt;®&lt;/sup&gt;</strong> ir Follicular Lymphoma</td>
<td><strong>ACZ885</strong> Adjuvant NSCLC</td>
</tr>
<tr>
<td></td>
<td>**Lucentis®&lt;sup&gt;c&lt;/sup&gt;<strong>ROP&lt;sup&gt;d&lt;/sup&gt;</strong></td>
<td><strong>LA-EP2006 (pegfilgrastim, US)</strong> Chemotherapy-induced neutropenia and others (same as originator)</td>
<td><strong>Xolair® Nasal Polyps</strong></td>
<td><strong>ACZ885</strong> 1st Line NSCLC</td>
</tr>
<tr>
<td>**Promacta®&lt;sup&gt;c&lt;/sup&gt;**Revolade®&lt;sup&gt;c&lt;/sup&gt;<strong>SAA 1st line</strong></td>
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<td></td>
<td><strong>Kayriah™</strong></td>
<td><strong>KAF156</strong> Malaria</td>
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<td><strong>ACZ885</strong> 2nd Line NSCLC</td>
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<td><strong>LHW090</strong> Resistant hypertension</td>
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<td><strong>BYM338</strong> Sarcopenia</td>
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</tbody>
</table>

### Combination abbreviations:

- fulv fulvestrant
- tmx tamoxifen
- gsn gosennin
- NSAI Non-steroidal aromatase inhibitor
- Tat Tafinlar® (dabrafenib)
- Mek Mekinist® (trametinib)

### Notes:

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. Neovascular age-related macular degeneration
8. Multi-drug resistant
9. Breast cancer
10. Retinopathy of prematurity
11. Non-Hodgkin’s lymphoma
12. Non-radiographic axial spondyloarthritis
13. Preserved ejection fraction
14. Graft-versus-host disease
15. Neuroendocrine tumors
16. Chronic spontaneous urticaria / chronic idiopathic urticaria
17. Pneumonic arthritis head-to-head study versus adalimumab
18. Non-alcoholic steatohepatitis
19. Arising spondylitis head-to-head study versus adalimumab
20. Acute myeloid leukemia
21. Chronic Obstructive Pulmonary Disease
22. Secondary Progressive Multiple Sclerosis

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- EU submitted, approved in US.
- US filing, approved in EU.
- US filing, submitted in EU.
- Lubris LLC transaction announced in April 2017.
- Conatus transaction for exclusive global license for emricasan announced in May 2017.
## Agenda

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
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</thead>
<tbody>
<tr>
<td>13:30 – 14:00</td>
<td>Registration</td>
</tr>
<tr>
<td>14:00 – 14:30</td>
<td>Introduction</td>
</tr>
<tr>
<td><strong>14:30 – 15:15</strong></td>
<td><strong>RTH258</strong></td>
</tr>
<tr>
<td>15:15 – 15:45</td>
<td>AMG 334</td>
</tr>
<tr>
<td>15:45 – 16:15</td>
<td>Break</td>
</tr>
<tr>
<td>16:15 – 17:00</td>
<td>Cosentyx®</td>
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<tr>
<td>17:00 – 17:30</td>
<td>ACZ885</td>
</tr>
<tr>
<td>17:30 – 18:00</td>
<td>Q&amp;A session</td>
</tr>
<tr>
<td>18:00</td>
<td>Cocktail with management</td>
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</table>
Left untreated, age-related macular degeneration (nAMD) can lead to blindness

Left untreated, nAMD can quickly lead to complete loss of central vision, leaving the patient unable to read, drive or recognize familiar faces.

Currently approved anti-VEGF therapies require monthly or bimonthly intravitreal (IVT) injections and frequent clinical assessment to monitor patient response to treatment.

Source: http://www.allaboutvision.com/conditions/amd.htm; site accessed October 9th 2017
What happens in nAMD?

Abnormal blood vessels form underneath the macula, the central area of the retina responsible for sharp vision.

These blood vessels leak fluid and blood into the eye, ultimately causing damage to the retina.

Can quickly lead to complete loss of central vision.
Normal retina and OCT scan

Macula: responsible for central vision for reading, driving, identifying faces

Image courtesy of Dr. Pravin Dugel

1. CST – central subfield thickness
OCT scan of an nAMD$^1$ patient showing IRF$^2$, SRF$^3$ and abnormal CST

1. nAMD – neovascular age-related macular degeneration   2. IRF – intraretinal fluid   3. SRF – subretinal fluid

Image courtesy of Dr. Pravin Dugel

1. nAMD – neovascular age-related macular degeneration   2. IRF – intraretinal fluid   3. SRF – subretinal fluid
Disease control by addressing fluid recurrence

Most important factors indicating recurrent nAMD disease activity in the maintenance phase

<table>
<thead>
<tr>
<th>Factor</th>
<th>US (%)</th>
<th>Intl (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subretinal fluid recurrence (SRF)</td>
<td>48.0%</td>
<td>46.6%</td>
</tr>
<tr>
<td>Intraretinal fluid recurrence (IRF)</td>
<td>34.5%</td>
<td></td>
</tr>
<tr>
<td>Macular hemorrhage</td>
<td>9.0%</td>
<td>13.1%</td>
</tr>
<tr>
<td>Loss of vision</td>
<td>3.9%</td>
<td>9.4%</td>
</tr>
</tbody>
</table>

Sources: 1. ASRS Preferences and Trends (PAT) membership survey 2017.
RTH258 (brolucizumab): the smallest known active unit of an antibody that allows for concentrated molar dosing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Unlicensed bevacizumab</th>
<th>Aflibercept</th>
<th>Ranibizumab</th>
<th>Brolucizumab</th>
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<tbody>
<tr>
<td>Format¹-⁵</td>
<td>Full antibody (IgG1)</td>
<td>VEGFR1/2-Fc fusion protein</td>
<td>Fab fragment</td>
<td>single-chain antibody fragment</td>
</tr>
<tr>
<td>Molecular structure</td>
<td><img src="Diagram1.png" alt="Diagram" /></td>
<td><img src="Diagram2.png" alt="Diagram" /></td>
<td><img src="Diagram3.png" alt="Diagram" /></td>
<td><img src="Diagram4.png" alt="Diagram" /></td>
</tr>
<tr>
<td>Molecular weight¹-⁵</td>
<td>≈ 149 kDa</td>
<td>97-115 kDa*</td>
<td>≈ 48 kDa</td>
<td>26 kDa</td>
</tr>
<tr>
<td>Clinical dose²,³,⁵-⁷</td>
<td>1.25 mg</td>
<td>2.00 mg</td>
<td>0.50 mg</td>
<td>6.00 mg</td>
</tr>
<tr>
<td>Equivalent molar dose</td>
<td>0.4-0.5</td>
<td>1.0</td>
<td>0.5-0.6</td>
<td>11.2-13.3</td>
</tr>
</tbody>
</table>

CH - constant heavy; CL - constant light; Fab - fragment, antigen-binding; Fc - fragment crystalizable; IgG - immunoglobulin G; VEGFR - vascular endothelial growth factor receptor; VH - variable heavy; VL - variable light.

* Molecular weight expressed as a range to reflect glycosylation status.

HAWK and HARRIER Phase 3 studies to assess q12w/q8w dosing RTH258 vs. q8w aflibercept

nAMD Phase 3 trial design
Trials designed to show differentiation vs. aflibercept

- 92 weeks (both trials)
- Brolucizumab 3 mg (q12w or q8w)*
- Brolucizumab 6 mg (q12w or q8w)*
- Aflibercept 2 mg (q8w)

- Brolucizumab 6 mg (q12w or q8w)*
- Aflibercept 2 mg (q8w)
RTH258: Baseline characteristics of HAWK and HARRIER studies were well-balanced

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>HAWK</th>
<th></th>
<th>HAWK</th>
<th>HARRIER</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Brolucizumab 3 mg (n = 358)</td>
<td>Brolucizumab 6 mg (n = 360)</td>
<td>Aflibercept 2 mg (n = 360)</td>
<td>Brolucizumab 6 mg (n = 370)</td>
<td>Aflibercept 2 mg (n = 369)</td>
</tr>
<tr>
<td>Age, mean (SD), years</td>
<td>76.7 (8.28)</td>
<td>76.7 (8.95)</td>
<td>76.2 (8.80)</td>
<td>74.8 (8.58)</td>
<td>75.5 (7.87)</td>
</tr>
<tr>
<td>Females, n (%)</td>
<td>210 (58.7)</td>
<td>205 (56.9)</td>
<td>194 (53.9)</td>
<td>210 (56.8)</td>
<td>212 (57.5)</td>
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<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>White</td>
<td>302 (84.4)</td>
<td>285 (79.2)</td>
<td>287 (79.7)</td>
<td>340 (91.9)</td>
<td>341 (92.4)</td>
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<tr>
<td>Asian</td>
<td>44 (12.3)</td>
<td>61 (16.9)</td>
<td>53 (14.7)</td>
<td>22 (5.9)</td>
<td>23 (6.2)</td>
</tr>
<tr>
<td>BCVA, mean (SD), letters</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 55 letters</td>
<td>61.0 (13.57)</td>
<td>60.8 (13.66)</td>
<td>60.0 (13.92)</td>
<td>61.5 (12.59)</td>
<td>60.8 (12.93)</td>
</tr>
<tr>
<td>56-70 letters</td>
<td>109 (30.4)</td>
<td>101 (28.1)</td>
<td>116 (32.2)</td>
<td>102 (27.6)</td>
<td>107 (29.0)</td>
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<tr>
<td>≥ 71 letters</td>
<td>138 (38.5)</td>
<td>157 (43.6)</td>
<td>153 (42.5)</td>
<td>171 (46.2)</td>
<td>170 (46.1)</td>
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<tr>
<td>CST, mean (SD), μm</td>
<td>466.6 (167.42)</td>
<td>463.1 (166.62)</td>
<td>457.9 (146.37)</td>
<td>473.6 (171.39)</td>
<td>465.3 (151.21)</td>
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<td>Type of CNV, n (%)</td>
<td></td>
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<td></td>
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<tr>
<td>Predominantly classic</td>
<td>122 (34.1)</td>
<td>113 (31.4)</td>
<td>116 (32.3)</td>
<td>154 (41.6)</td>
<td>144 (39.5)</td>
</tr>
<tr>
<td>Minimally classic</td>
<td>32 (8.9)</td>
<td>39 (10.8)</td>
<td>34 (9.5)</td>
<td>33 (8.9)</td>
<td>34 (9.3)</td>
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<tr>
<td>Occult</td>
<td>204 (57.0)</td>
<td>208 (57.8)</td>
<td>209 (58.2)</td>
<td>183 (49.5)</td>
<td>187 (51.2)</td>
</tr>
<tr>
<td>Lesion area associated with CNV, mean (SD), mm²</td>
<td>4.5 (4.70)</td>
<td>4.6 (4.08)</td>
<td>4.4 (3.72)</td>
<td>2.6 (2.76)</td>
<td>3.0 (3.96)</td>
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<tr>
<td>Presence of fluid, n (%)</td>
<td></td>
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<tr>
<td>Subretinal fluid</td>
<td>244 (68.3)</td>
<td>250 (69.6)</td>
<td>245 (68.1)</td>
<td>251 (67.8)</td>
<td>268 (72.6)</td>
</tr>
<tr>
<td>Intraretinal fluid</td>
<td>196 (54.9)</td>
<td>194 (53.9)</td>
<td>194 (54.0)</td>
<td>149 (40.4)</td>
<td>139 (37.7)</td>
</tr>
<tr>
<td>Sub-RPE fluid</td>
<td>147 (41.2)</td>
<td>168 (46.9)</td>
<td>158 (44.0)</td>
<td>125 (33.8)</td>
<td>127 (34.4)</td>
</tr>
</tbody>
</table>

BCVA, best corrected visual acuity; CNV, choroidal neovascularization; CST, central subfield thickness; RPE, retinal pigmented epithelium.
All RTH258 patients start on q12w immediately following loading; if disease activity is seen, interval adjusted to q8w. Aflibercept is dosed every 8-weeks per label.

### Matched regimen head-to-head assessment

<table>
<thead>
<tr>
<th>Week</th>
<th>First disease activity assessment</th>
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<tr>
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<td>24</td>
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<td>32</td>
<td>36</td>
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<td>80</td>
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<td>88</td>
<td>92</td>
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<td>96</td>
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</tr>
</tbody>
</table>

### q12w/q8w dosing with brolucizumab; q8w dosing with aflibercept

<table>
<thead>
<tr>
<th>Week</th>
<th>Primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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<tr>
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<td>92</td>
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<tr>
<td>96</td>
<td></td>
</tr>
</tbody>
</table>

### Disease Activity Assessments

**Matched regimen head-to-head assessment**

- **Brolucizumab 3.0/6.0 mg q12w/q8w**
  - Interval adjusted to q8w if disease activity observed
- **Aflibercept 2.0 mg q8w**

**Primary endpoint**

**HAWK: 1:1:1 randomization**

**HARRIER: 1:1 randomization**

*Additional assessments and potential dosing interval adjustments occurred at Weeks 28, 40, 52, 64, 76, and 88 in HARRIER only.
Significantly fewer patients on RTH258 (brolucizumab) had signs of disease activity at the head-to-head assessment.

Disease activity as assessed by masked investigator at week 16*

Patients with disease activity, %

<table>
<thead>
<tr>
<th></th>
<th>Brolucizumab 3 mg (n = 358)</th>
<th>Brolucizumab 6 mg (n = 360)</th>
<th>Aflibercept 2 mg (n = 360)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P = 0.0398</strong></td>
<td>27.4</td>
<td>30%</td>
<td>33.5</td>
</tr>
<tr>
<td><strong>P = 0.0022</strong></td>
<td>23.5</td>
<td>23.5</td>
<td>30%</td>
</tr>
<tr>
<td><strong>P = 0.0022</strong></td>
<td>21.9</td>
<td>31.4</td>
<td>30%</td>
</tr>
</tbody>
</table>

*Prespecified secondary endpoint in both HAWK and HARRIER with confirmatory analysis in HAWK (brolucizumab 6 mg vs aflibercept 2 mg). Week 16 disease activity assessed by: decrease in BCVA of > 5 letters compared with baseline, decrease in BCVA of > 3 letters and CST increase > 75µm compared with week 12, decrease in BCVA of > 5 letters due to neovascular AMD disease activity compared with week 12, new or worse intraretinal cysts (IRC) / intraretinal fluid (IRF) compared with week 12.
RTH258 (brolucizumab) achieved superiority – fewer patients with presence of retinal fluids, key markers of disease activity

Patients with IRF\(^1\) and/or SRF\(^2\), \%*

<table>
<thead>
<tr>
<th></th>
<th>Week 16</th>
<th>Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brolucizumab 3 mg (n = 358)</td>
<td>34</td>
<td>31</td>
</tr>
<tr>
<td>Brolucizumab 6 mg (n = 360)</td>
<td>52</td>
<td>45</td>
</tr>
<tr>
<td>Aflibercept 2 mg (n = 360)</td>
<td>42</td>
<td>45</td>
</tr>
</tbody>
</table>

\(P = .0028\) \(\text{vs} \text{.} .0001\) \(\text{vs} \text{.} .0019\) \(\text{vs} \text{.} .0001\)

*Prespecified secondary endpoint in both HAWK and HARRIER with confirmatory analysis in HAWK (brolucizumab 6 mg vs aflibercept 2 mg).  
1. IRF – Intraretinal fluid  
2. SRF – Subretinal fluid
Fewer patients on RTH258 (brolucizumab) had fluid in the deepest layer of the retina (sub-RPE¹)

Patients with fluid (sub-RPE¹) present, %*

<table>
<thead>
<tr>
<th>Week 16</th>
<th>Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brolucizumab 3 mg</strong> (n = 358)</td>
<td><strong>Brolucizumab 6 mg</strong> (n = 360)</td>
</tr>
<tr>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td>19</td>
<td>14</td>
</tr>
</tbody>
</table>

*Prespecified secondary endpoint  ¹RPE – Retinal pigment epithelium

P = .0270  P = .0021  P = .1534  P = .0024

P = .0041  P = .0010

30% 33% 41%
RTH258 delivered superior reductions in retinal thickness (CST), marker of fluid accumulation, versus aflibercept in both the head-to-head and maintenance phases.

**Graphs:**
- **Matched head-to-head assessments**
  - Brolucizumab 3 mg (n = 358)
  - Brolucizumab 6 mg (n = 360)
  - Afiblercept 2 mg (n = 360)
  - CST change from baseline, µm, LS mean (SE)

  - **HAWK**
    - P = .0016*
  - **HARRIER**
    - P = .0023*#

- **Majority of brolucizumab patients maintained on a q12w dosing interval**
  - Brolucizumab 6 mg (n = 370)

  - CST change from baseline, µm, LS mean (SE)

  - **HAWK**
    - P = .001*
  - **HARRIER**
    - P = .001*#

---

CST = central subfield thickness; *pre-specified secondary endpoint in both HAWK and HARRIER with confirmatory superiority analysis in HAWK (brolucizumab 6 mg vs aflibercept 2 mg); *P < .05 for change in CST from baseline averaged over period of week 36 – 48.
The majority of RTH258 patients were exclusively maintained on a q12w dosing interval immediately following loading phase through week 48

Patients on q12w interval at week 48, %

<table>
<thead>
<tr>
<th>Brolucizumab 3mg</th>
<th>Brolucizumab 6mg</th>
<th>Brolucizumab 3mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>52%</td>
<td>57%</td>
<td>52%</td>
</tr>
</tbody>
</table>
Overall safety of RTH258 was comparable to aflibercept and consistent with other anti-VEGF drugs

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>HAWK</th>
<th>HARRIER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brolucizumab 3 mg</strong>&lt;br&gt;(n = 358)</td>
<td><strong>Brolucizumab 6 mg</strong>&lt;br&gt;(n = 360)</td>
<td><strong>Aflibercept 2 mg</strong>&lt;br&gt;(n = 360)</td>
</tr>
<tr>
<td>Ocular adverse events in study eye, n (%)</td>
<td>175 (48.9)</td>
<td>179 (49.7)</td>
</tr>
<tr>
<td>Nonocular adverse events, n (%)</td>
<td>241 (67.3)</td>
<td>232 (64.4)</td>
</tr>
<tr>
<td>Serious adverse events, total, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study eye</td>
<td>52 (14.5)</td>
<td>59 (16.4)</td>
</tr>
<tr>
<td>Nonocular</td>
<td>5 (1.4)</td>
<td>11 (3.1)</td>
</tr>
<tr>
<td></td>
<td>47 (13.1)</td>
<td>47 (13.1)</td>
</tr>
<tr>
<td>Patients with ≥ 15 letter loss at week 48, %</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>4 (1.1)</td>
<td>4 (1.1)</td>
</tr>
<tr>
<td>Systemic ATE, n (%)</td>
<td>14 (3.9)</td>
<td>9 (2.5)</td>
</tr>
</tbody>
</table>

ATE, arterial thromboembolic events.

* A minor numerical error was corrected; this has no impact on the safety conclusion
RTH258 demonstrated an improved profile for disease control and convenience compared to aflibercept pivotal studies

Better reduction in retinal fluids: compared to aflibercept, brolucizumab with\(^1\):

- Significantly fewer patients with retinal fluid (IRF and/or SRF), an indicator of disease control
- Fewer patients with fluid in the deepest layer of the retina (sub-RPE)
- Superior reductions in retinal thickness (CST), an indicator of disease control

<table>
<thead>
<tr>
<th>Brolucizumab (HAWK &amp; HARRIER)</th>
<th>Aflibercept (VIEW-1 &amp; VIEW-2)(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement in visual acuity</td>
<td>Non-inferior to aflibercept</td>
</tr>
<tr>
<td>Less frequent administration</td>
<td>Every 12 weeks(^2)</td>
</tr>
<tr>
<td>Less frequent dose/interval adjustment</td>
<td>• Regular injection schedule every 12 or 8 weeks</td>
</tr>
<tr>
<td></td>
<td>• First prospectively defined trials showing evidence of q12 interval immediately following loading</td>
</tr>
<tr>
<td></td>
<td>• Treat and extend regimen in year 2(^4)</td>
</tr>
<tr>
<td></td>
<td>• Exploratory analysis of PRN(^5) 12-week dosing in VIEW year 2; patients were switched back to 8-week regimen (data does not support claims or regulatory filing)</td>
</tr>
</tbody>
</table>

\(^1\) Data on file, HAWK & HARRIER Ph3 results  \(^2\) Majority of patients on a q12w interval immediately following loading  \(^3\) Ophthalmology 2012;119:2537-2548  \(^4\) According to label  \(^5\) PRN – Pro re nata
Important unmet needs remain in nAMD with current anti-VEGF therapies

Current anti-VEGF therapies may compromise efficacy in real life due to under treatment

- Treatment burden can stress clinic capacity and impact patient adherence, which can result in under-utilization
- Under-utilization is well documented: multinational, retrospective, observational study suggests real world injection rates of 5 in year 1, resulted in vision decline
- Fewer injections may compromise efficacy compared to results seen with labeled regimen

Strong unmet need for new treatments that have a longer duration of action, to allow for longer time intervals between injections

Physicians seek retinal fluid resolution, as a majority consider fluid recurrence a major indicator of recurrent neovascular AMD

RTH258 demonstrated greater fluid resolution with less frequent dosing vs. aflibercept, with the potential to address unmet needs versus current therapies

RTH258 showed greater fluid resolution with fewer injections vs. aflibercept in secondary endpoints in HAWK and HARRIER studies

- Significantly fewer patients treated with RTH258 had presence of retinal fluids, key markers of disease activity, in comparison to aflibercept

- The majority of RTH258 patients were exclusively maintained on a q12w dosing interval immediately following loading phase through week 48

Illustration: Dosing regimen referenced according to label for aflibercept, brolucizumab based on q12w regime in HAWK & HARRIER; fluid resolution defined as presence of retinal fluids, key markers of disease activity (prespecified secondary endpoint in both HAWK and HARRIER with confirmatory analysis in HAWK; brolucizumab 6 mg vs aflibercept 2 mg).
Opportunity to enter attractive US market

Large market
nAMD, DME and RVO market size (USD bn)

US market anti-VEGF therapies

- nAMD accounts for 2/3 of US 2016 anti-VEGF sales of USD 4.8bn
- Anti-VEGF therapy is covered by Medicare Part B (outside the pharmacy benefit managed by PBMs)
- Unlicensed Avastin® volume market share in 2016 was at c. 45%, expect limited impact from biosimilars (expected earliest in in 2021)

Source: Evaluate Pharma, Oct’17  All trademarks are the property of their respective owners
RTH258 next steps

• Further details of the HAWK and HARRIER trials to be presented at congresses in 2018

• Plan to discuss the data with HAs at pre-submission meetings in Q2 2018

• Target filing of nAMD indication in Dec 2018: upon completion of activities and documentation to support the commercial scale up of the product

• In parallel, we are preparing clinical trials to start in other indications, such as DME (H1 2018) and RVO (H2 2018)
Agenda

13:30 – 14:00  Registration
14:00 – 14:30  Introduction
14:30 – 15:15  RTH258
15:15 – 15:45  AMG 334
15:45 – 16:15  Break
16:15 – 17:00  Cosentyx®
17:00 – 17:30  ACZ885
17:30 – 18:00  Q&A session
18:00  Cocktail with management
Three debated topics about migraine and anti-CGRP therapy

- "Just a headache", Multiple existing treatment options
- Modest
- Speed of onset, dosing convenience
- Disease burden
- Therapeutic benefit of CGRP inhibition
- What it takes to be successful
- Debilitating & disabling, many sub-optimally treated
- Life-changing
- Sustained & consistent prevention
Migraine is a debilitating disease affecting millions, imposing high societal burden

>10% of the global adult population

...one of the top 10 highest causes of disability globally, 4th among women...

...highest prevalence with people in their prime working years (ages 30 to 39 years)

The estimated cost of migraine is EUR 27 billion per year in Europe
The estimated healthcare and lost productivity cost is 36 USD billion per year in US

4. Lipton RB, Neurology. 2007;68(5):343-349
5. Migraine Research Foundation accessed October 23 2017
Localization of CGRP receptors in migraine pathophysiology
Today’s prophylaxis treatments are all re-purposed and mainly prescribed off-label, with tolerability issues

<table>
<thead>
<tr>
<th>Category</th>
<th>Compound (drug class)</th>
<th>Contraindications &amp; common adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-epileptic</td>
<td>Topiramate</td>
<td>Paresthesia, cognitive symptoms, weight loss, depression, dizziness, teratogenicity</td>
</tr>
<tr>
<td></td>
<td>Valproate, gabapentin</td>
<td>Hepatotoxicity, teratogenicity, weight gain, tremor, confusion, thrombocytopenia</td>
</tr>
<tr>
<td>Anti-hypertensive</td>
<td>Beta-Blocker: Propranolol/metoprolol(^1)</td>
<td>Asthma, diabetes, bradycardia, hypotension, fatigue, depression, dizziness</td>
</tr>
<tr>
<td></td>
<td>CCBs: flunarizine(^3), verapamil</td>
<td>Depression, drowsiness, weight gain, changes in appetite, rhinitis, dizziness, tremor, bradycardic arrhythmia, vertigo</td>
</tr>
<tr>
<td></td>
<td>ACEi/ARB: lisinopril, candesartan</td>
<td>Cough, dizziness/vertigo, headache, teratogenicity, angioedema, anaphylactoid reactions</td>
</tr>
<tr>
<td>Anti-depressants</td>
<td>Tricyclics(^2): amitriptyline, nortriptiline</td>
<td>Anticholinergic symptoms, weight gain, arrhythmia, glaucoma, dizziness</td>
</tr>
<tr>
<td></td>
<td>SSRI/SNRI: vilafaxine, duloxetine</td>
<td>Insomnia, dizziness, hypertension, weight change, visual disturbances, sexual dysfunction, sweating, suicidality/suicidal ideation</td>
</tr>
<tr>
<td>Other</td>
<td>Botox (Botulinum toxin)</td>
<td>Asthenia, myalgia, muscle weakness, facial paresis, pruritus, hypersensitivity</td>
</tr>
</tbody>
</table>

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; SNRIs, serotonin–norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.  
1. Metoprolol is only indicated for migraine prophylaxis in Europe, not in the US  
2. Amitriptyline has been recently approved across the EU in a European harmonisation procedure  
3. Flunarizine licensed for migraine prophylaxis in some EU countries

Available treatment options result in high discontinuation rates, and risk of medication overuse

>75% of chronic migraine patients discontinue treatment by 6 months\(^1\)

Vicious cycle: medication overuse headache\(^2\)

Existing preventative treatments have serious drawbacks, resulting in frequent treatment discontinuation

Lack of effective prophylaxis may lead to Medication Overuse (MO) of acute pain medication

MO can lead to a vicious cycle of MOH, requiring detoxification

Urgent need for new therapies with sustained efficacy and favorable safety

Variability in assessing key migraine outcomes limits cross-trial comparisons

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>How it is evaluated</th>
<th>Usage and remarks</th>
</tr>
</thead>
</table>
| Reduction of monthly migraine days (MMD) | • Absolute change from baseline  
• Relative difference to placebo at a pre-defined timepoint | • Primary regulatory endpoint  
• Limited relevance for clinicians  
• Cross trial comparisons are limited by varying ‘migraine’ definitions, placebo rates, timepoint and assessment intervals |
| 50% Responder Rate (additionally could be assessed at 75% or 100%) | • Absolute % of patients achieving a response who experienced at least 50% reduction in the MMD compared to baseline  
• Relative comparison to placebo at a pre-defined timepoint by odds ratio | • Often used as (key) secondary endpoint  
• Relevant clinical measure for physicians in clinical practice  
• Cross trial comparisons are limited due to the underlying variable placebo rates, timepoint and assessment intervals |

Assessment of key migraine outcomes should consider both endpoints and the relative comparison to placebo by odds ratio.
AMG 334 (erenumab) has shown consistent efficacy across the spectrum of migraine

Chronic migraine (CM): Study 295

Baseline mean monthly migraine days
Placebo: 18.2
70mg: 17.9
140mg: 17.8

Primary Endpoint

Baseline mean monthly migraine days
Placebo: 18.2
70mg: 17.9
140mg: 17.8

50% Responder Rate

<table>
<thead>
<tr>
<th>Arm</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>24%</td>
</tr>
<tr>
<td>70 mg erenumab</td>
<td>40%</td>
</tr>
<tr>
<td>140 mg erenumab</td>
<td>41%</td>
</tr>
</tbody>
</table>

Episodic migraine (EM)
Consistently, efficacy was demonstrated in the EM trials

Responders had ~70% reduction in chronic migraine (CM) days per month¹

Chronic migraine (CM): Study 295

Episodic migraine (EM)
Similar results were also seen when a comparable analysis was done in the EM pivotal trial

¹ Responders’ are subjects who achieved at least 50% reduction from baseline on monthly migraine days (MMD) at primary endpoint (month 3). <50% Responders are subjects who did not achieve 50% reduction from baseline on MMD at primary endpoint. Post-hoc analysis from studies 295 showing erenumab 140 mg. Data on file.
AMG 334 (erenumab) has shown consistent efficacy even in the most difficult to treat patients

Subgroup of patients having failed previous prevention treatment (CM)
Reduction in monthly migraine days

Subgroup of patients with medication overuse at baseline (stratified, CM subjects)
Reduction in monthly days with acute migraine-specific medication use (triptans and ergot derivatives)

Patients with ≥2 prior treatment failures:
placebo (N=142); erenumab 70 mg (N=93); erenumab 140 mg (N=92)

Patients with recent medication overuse:
placebo (N=113); erenumab 70 mg (N=78); erenumab 140 mg (N=77)

*p<0.001; Ashina et al, Pre-specified subgroup analysis. PR1046 presented at EAN; Diener H et al, PR1048 presented at EAN.
1 out of every 4 patients were completely migraine free (100% response) at end of month 15\(^1\), demonstrating sustained efficacy.

Responder rate with AMG 334 (erenumab) 70 mg after 15 months (episodic migraine)

<table>
<thead>
<tr>
<th>Responder Rate</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>50% responder</td>
<td>65%</td>
</tr>
<tr>
<td>75% responder</td>
<td>42%</td>
</tr>
<tr>
<td>100% responder</td>
<td>26%</td>
</tr>
</tbody>
</table>

Sustained efficacy has also been seen in chronic migraine after one year (data not presented yet)

---

1. Ashina M et al. 2017 Neurology. Pre-planned interim analysis of 5-year open-label extension study of patients completing Ph2 20120178 study (in EM), conducted once all patients completed at least 52 weeks of follow-up and assessed at weeks 61-64 at the 70 mg dose.
AMG 334 (erenumab) shows a placebo-like safety and tolerability profile

- >2,600 patients were studied in the development program
- High retention was seen in pivotal trials over 3 or 6 months with 90% to 95% of patients completing
- Pooled analysis across the 4 key clinical trials after 12 weeks have confirmed that erenumab has a similar safety and tolerability profile to placebo

### Pooled analysis across 4 clinical trials

Details on clinical trial program can be found in appendix

<table>
<thead>
<tr>
<th>All treatment-emergent AE</th>
<th>Placebo (n=1,043)</th>
<th>70 mg erenumab (n=893)</th>
<th>140 mg erenumab (n=507)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All treatment-emergent AE</td>
<td>49.0%</td>
<td>47.3%</td>
<td>46.0%</td>
</tr>
<tr>
<td>Serious AE</td>
<td>1.5%</td>
<td>1.7%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Leading to discontinuation due to AE</td>
<td>1.0%</td>
<td>1.7%</td>
<td>1.8%</td>
</tr>
</tbody>
</table>

AE identified are injection site reactions, pruritus, constipation and muscle spasm. All <5% and usually of mild severity.  
1. Data on file, Amgen
Assessment of safety areas of specific interest have shown favorable results

CV safety study in stable angina patients
- AMG 334 did not adversely affect exercise time, a surrogate of underlying myocardial ischemia
- No difference compared to placebo:
  - on time to ≥1 mm ST-segment depression
  - on time to exercise-induced angina

Injection site reactions data
- AMG 334 is well tolerated locally
- Overall low amount of injection site reactions and <2% difference vs placebo in pooled safety data across all studies\(^1\)
- Fully human mAb showing low hypersensitivity and immunogenicity

Survival Probability

<table>
<thead>
<tr>
<th>Event Free Time in Seconds</th>
<th>0</th>
<th>200</th>
<th>400</th>
<th>600</th>
<th>800</th>
<th>1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (N=1043)</td>
<td>44</td>
<td>40</td>
<td>28</td>
<td>10</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>70 mg erenumab (n=893)</td>
<td>44</td>
<td>42</td>
<td>26</td>
<td>10</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>140 mg erenumab (n=507)</td>
<td>44</td>
<td>42</td>
<td>26</td>
<td>10</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Number of Patients at Risk
1. Data on file - Amgen

Injection site reactions

- Placebo
- 70 mg erenumab
- 140 mg erenumab

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=1043)</th>
<th>70 mg erenumab (n=893)</th>
<th>140 mg erenumab (n=507)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.2%</td>
<td>5.0%</td>
<td>4.5%</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) Data on file - Amgen
While ~40% of severe migraine patients are prophylactically treated today, many will seek new options due to sub-optimal efficacy and poor tolerability.

### Target population of EU5

<table>
<thead>
<tr>
<th>Total prevalence of migraine</th>
<th>33</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosed</td>
<td>19</td>
<td>58%</td>
</tr>
<tr>
<td>Intermediate- to high-frequency and chronic migraine</td>
<td>10</td>
<td>31%</td>
</tr>
<tr>
<td>Prophylactically treated</td>
<td>4</td>
<td>12%</td>
</tr>
</tbody>
</table>

### Target population of US

<table>
<thead>
<tr>
<th>Total prevalence of migraine</th>
<th>37</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosed</td>
<td>25</td>
<td>67%</td>
</tr>
<tr>
<td>Intermediate- to high-frequency and chronic migraine</td>
<td>10</td>
<td>27%</td>
</tr>
<tr>
<td>Prophylactically treated</td>
<td>3.5</td>
<td>10%</td>
</tr>
</tbody>
</table>

AMG 334 (erenumab) – potentially life-changing medication for a debilitating disease

Unique approach
- First and only to target and block the CGRP-receptor
- Only fully human anti-CGRP mAb

Sustained and consistent prevention
- Chronic migraine patients gained up to a week back of their life each month\(^1\)
- At 1 year\(^2\), 2/3 of episodic migraine patients had at least a 50% reduction in their migraine days with 1 out of 4 being completely migraine free

Unique & robust data package, even in the difficult to treat patients
- >2,600 patients; 5 year on-going extension
- Strong efficacy in prior treatment failures, medication overuse patients

Placebo-like safety and tolerability
- Only anti-CGRP mAb that demonstrated no increased CV risk\(^3\)
- Almost no injection site reactions

1. Tepper S, Lancet Neurology 16(6), June 2017, 425–434
Appendix
## Clinical program overview (key studies)

<table>
<thead>
<tr>
<th>Study</th>
<th># of pts</th>
<th>Design</th>
<th>Duration</th>
<th>Doses (mg)</th>
<th>Main objective</th>
<th>Primary endpoint (PEP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20120296 (STRIVE)</td>
<td>955</td>
<td>DB, pbo-controlled</td>
<td>24 weeks DB 28 weeks ATP</td>
<td>0 70 140</td>
<td><strong>Pivotal EM trial</strong></td>
<td>MMD reduction in weeks 13-24</td>
</tr>
<tr>
<td>Phase 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20120295</td>
<td>667</td>
<td>DB, pbo-controlled</td>
<td>12 weeks DB 52 weeks OLE*</td>
<td>0 70 140</td>
<td><strong>Pivotal CM trial</strong></td>
<td>MMD reduction in weeks 9-12</td>
</tr>
<tr>
<td>Phase 2¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20120297 (ARISE)</td>
<td>577</td>
<td>DB, pbo-controlled</td>
<td>12 weeks DB 40 weeks OLE</td>
<td>0 70 -</td>
<td><strong>Supportive ph3 EM trial / MPFID validation</strong></td>
<td>MMD reduction in weeks 9-12</td>
</tr>
<tr>
<td>Phase 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20120178</td>
<td>483</td>
<td>DB, pbo-controlled</td>
<td>12 weeks DB 256 weeks OLE</td>
<td>0 7, 21 70</td>
<td><strong>Dose finding EM</strong></td>
<td>MMD reduction in weeks 9-12</td>
</tr>
<tr>
<td>Phase 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Other noteworthy studies (list not complete)**

<table>
<thead>
<tr>
<th>Study</th>
<th># of pts</th>
<th>Design</th>
<th>Duration</th>
<th>Doses (mg)</th>
<th>Main objective</th>
<th>Primary endpoint (PEP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAMG334A2301</td>
<td>246</td>
<td>DB, pbo-controlled</td>
<td>12 weeks DB 52 weeks OLE</td>
<td>0 - 140</td>
<td><strong>Ph3b study in 2-4 treatment failure patients</strong></td>
<td>50% responder rate in weeks 9-12</td>
</tr>
<tr>
<td>(LIBERTY)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20140254</td>
<td>88</td>
<td>DB, pbo-controlled</td>
<td>1 day DB 12 weeks f/up</td>
<td>0 - 140 IV</td>
<td><strong>Effects in stable angina patients</strong></td>
<td>exercise time on the treadmill</td>
</tr>
<tr>
<td>(„treadmill“)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Initially set up as Ph2 study, amended to fulfill pivotal standards. Blue shaded studies are pivotal. DB: double-blind; ATP: active treatment phase; OLE: open-label extension; EM: episodic migraine; CM: chronic migraine; MMD: mean monthly migraine days.
Agenda

13:30 – 14:00  Registration
14:00 – 14:30  Introduction
14:30 – 15:15  RTH258
15:15 – 15:45  AMG 334
15:45 – 16:15  Break
16:15 – 17:00  Cosentyx®
17:00 – 17:30  ACZ885
17:30 – 18:00  Q&A session
18:00          Cocktail with management
Immune Suppression towards Targeted Intervention

- Initial focus: Rheumatoid Arthritis (RA), Crohn’s
- 2016 sales of USD 36bn in multiple indications

**Shortcomings of anti-TNF therapy**

**Efficacy:**
- 1st generation mAbs carry high immunogenicity
- Immune system is blocked upstream, with multiple options for escape
  → Large number of patients experience residual disease

**Safety:** Risk of serious infections and malignancies (boxed warning)

**Anti-TNFs mAbs**

- Take immunology from general immune suppression towards targeted intervention
- Initial focus: Rheumatoid Arthritis (RA), Crohn’s
- 2016 sales of USD 36bn in multiple indications

**Immunology at Novartis**

Search for more specific intervention for improved efficacy and safety:
- **Ilaris** (orphan rheumatology)
- **Cosentyx®** targeting the cornerstone cytokine IL-17A in psoriasis & spondyloarthritis

---

Psoriasis and spondyloarthritis: chronic auto-immune conditions with risk of long-term complications

Psoriasis (PsO) | Psoriatic arthritis (PsA) | Ankylosing spondylitis (AS)

Chronic, life-long auto-immune conditions driven by IL-17A

Significant daily symptom burden for patients:

- **Psoriasis**: scaly, itchy skin plaques – impact on quality of life
- **Psoriatic arthritis**: joint stiffness and pain – impacting daily living
- **Ankylosing spondylitis**: back pain and stiffness – impacting daily living

Long-term implications: irreversible damage

- **Psoriasis**: high inflammatory burden, potential joint damage
- **Psoriatic arthritis**: peripheral joint damage – potential disability
- **Ankylosing spondylitis**: spinal joint damage – fusing, long-term disability

References:

Spondyloarthritis (SpA) affects spine (axial SpA) and peripheral joints (peripheral SpA)

SpA disease background\textsuperscript{1,2,3}

- Family of inflammatory diseases that involve joints and entheses (where ligaments and tendons attach to bones)
- Strong genetic component: most common gene is HLA-B27, c.30 further genes have been associated with spondyloarthritis
- Main symptom in axial SpA is lower back pain; peripheral SpA causes pain and swelling of joints

Cosentyx® treatment goals: long-term relief of signs & symptoms, aiming for remission in PsA & AS

<table>
<thead>
<tr>
<th>Condition</th>
<th>Traditional agents</th>
<th>Aiming higher with Cosentyx®</th>
</tr>
</thead>
<tbody>
<tr>
<td>PsA</td>
<td>Often only partial relief of signs &amp; symptoms</td>
<td>Remission – inactive disease</td>
</tr>
<tr>
<td></td>
<td>Long-term efficacy questionable</td>
<td>• Resolution of signs &amp; symptoms</td>
</tr>
<tr>
<td>AS</td>
<td>Often only partial relief of signs &amp; symptoms</td>
<td>• Long-term inhibition of structural progression</td>
</tr>
<tr>
<td></td>
<td>Long-term efficacy questionable</td>
<td>• Early treatment to prevent irreversible damage and reduce impact of inflammation</td>
</tr>
<tr>
<td>Non-radiographic axial SpA</td>
<td>Limited current treatment options</td>
<td></td>
</tr>
<tr>
<td>(nrAxSpA)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Inhibiting the cornerstone inflammatory cytokine IL-17A is key

Cosentyx®: strong differentiation based on unique biology

Psoriasis

- Superiority to anti-TNF (Enbrel®) and Stelara®
- Sustained control of signs and symptoms (5-year landmark data)
- Strong data in joints (in psoriatic arthritis, ~ 1/3 of psoriasis population) and hard-to-treat manifestations
- Potential for disease modification

Spondyloarthritis

- Sustained control of signs and symptoms
- High level of enthesitis resolution
- No radiographic progression in psoriatic arthritis and ankylosing spondylitis
- Further building the evidence with ongoing studies

Fully human molecule with close to zero immunogenicity, very low injection site reactions

Focus today

3. Thaci D, et al. JAAD; 2015; 73, 3, 400–409
5. Bissonnette et al. Late Breaker Poster presentation, EADV 2016
8. Gottlieb A et al. JAAD 2017;76:70-80
9. Reich K et al. Ann Rheum Dis2016;75;suppl2
Low immunogenicity is critical for compelling, unrivalled long-term control of signs and symptoms

Cosentyx® demonstrates lower immunogenicity potential vs. competitors (in vitro assay)³

5 year, Ph3 data in psoriasis¹,²
Long-term sustained skin clearance

1. Bissonnette R., et al. late breaking abstract at EADV; September 13, 2017  
2. As observed; n, number of evaluable patients in the as observed analysis; PASI, Psoriasis Area and Severity Index score  
3. in healthy volunteer peripheral blood cells, Spindeldreher S., et al. abstract at EADV, 2017  
All trademarks are the property of their owners.
Enthesitis differentiates AS and PsA from RA

- Primary synovial membrane disease vs. enthesisial disease with secondary synovial membrane involvement
- Aids differential diagnosis of ankylosing spondylitis / psoriatic arthritis vs. rheumatoid arthritis

Enthesitis exists in both subclinical and clinical forms

Subclinical enthesitis

- Higher prevalence of enthesitis in psoriasis\(^8\)–\(^{10}\)
- No overt clinical symptoms but present on ultrasound\(^{11}\)
- Nail disease may be a visible indication of underlying asymptomatic enthesitis and consistently predicts PsA\(^{12,13}\)

Clinical enthesitis

- Characterized by pain (and swelling) at the entheses\(^1\)
- 56–79% of PsA subjects present with enthesitis in clinical trials\(^2\)–\(^7\)
- About 35% of overall PsA patients present with symptoms related to enthesitis\(^13\)

Enthesitis predicts development of SpA, leading to poor QoL outcomes and irreversible bone damage\(^{14}–^{16}\)

Cosentyx® blocks IL-17A, the cornerstone cytokine of enthesitis

NOTE: Multiple pathways exist for IL-17A production and this schematic does not show all IL-23 dependent and independent pathways.

Without early treatment, IL-17A-driven enthesitis leads to irreversible structural damage in AS and PsA

- **a)** IL-17 along with other relevant cytokines are produced from Th17 T cells, γδ T cells, ILC3, iNKTT cells, CD4/CD8 T cells, mast cells and neutrophil cells.
- **b)** Bone erosion precedes new bone formation in AS and PsA. IL-17, IL-22, TNFα, IL12-23 involved in erosion.
- **c)** IL-17 and IL-22 cytokines involved in new bone formation based on animal models.

**Signs and symptoms**

- Mechanical stress & genetics

**Structural damage**

- Bone erosion & new bone formation

---

1. Cosentyx Summary of Product Characteristics. 2017
Early targeting of IL-17A has the potential to change the course of disease in AS and PsA

Cosentyx® demonstrated effective long-term control of signs and symptoms in PsA and AS

**PsA:** Over 80% ACR20 response at 3 years¹⁻⁵
3-year data from FUTURE 1 Ph3 trial, anti-TNF-naïve population

**AS:** 80% ASAS20, 61% ASAS40 response at 4 years⁶,⁷
4-year data from MEASURE 1, Ph3 trial

**Signs & symptoms**
- Sustained ACR20/50/70 responder rates at 3 years¹,²,³
- Rapid & sustained pain relief shown in PsA ⁴

---

2. Novartis Data on File 2016. FUTURE 1 Data Tables; 14.2-1.9a, 14.2-7.9a, 14.2-12.8a
4. NCT02745080; 4 ACR responses shown as observed data from the FUTURE 1 study, in which patients received intravenous loading doses of secukinumab (anti–TNF-naïve population)
5. Mease P et al, SAT0470, EULAR Poster 2017
7. MEASURE 1 Study, ASAS. Assessment of Spondyloarthritis International Society; N, number of patients randomized. As observed data through Week 208; 10mg i.v. loading dose followed by 150mg subcutaneous
Cosentyx® has shown sustained improvement in the resolution of enthesitis in PsA

Long-term resolution of enthesitis\textsuperscript{1,2,3,4}

3 year data from FUTURE 1, Phase III trial

Measuring enthesitis:

- Based on standard tools (scores) assessing enthesitis at different points
- Enthesitis resolution represents a higher bar than enthesitis reduction shown by other agents

3. Mease P et al, SAT0470, EULAR Poster 2017
4. Resolution of enthesitis amongst those patients with these symptoms at baseline; multiple imputation; non-responder imputation (in patients entering extension trial)
Cosentyx® has strong data on structural progression in both PsA and AS

PsA: Inhibition of structural progression at 2 years

AS: No radiographic / structural progression at 4 years

1. Kavanaugh A, et al. Arthritis Care Res. 2016 [ePub ahead of print]; 2 Non-progression defined as a change in mTSS from baseline ≤0.5; overall population (observed data), data from the FUTURE1 study, in which patients received intravenous loading doses of secukinumab.


5. MEASURE 1 study: mSASSS, modified Stoke Ankylosing Spondylitis Spinal Score / No progression was defined as a mSASSS change change < 2 from baseline to Week 208 / 89.7% (IV–150 mg) and 93% (IV–75 mg) of Week 208 completers had Baseline and 4-year follow-up X-rays
Generating further evidence for sustained benefit

**SURPASS** – ankylosing spondylitis
2-year head-to-head study vs proposed biosimilar adalimumab allows comparative assessment of structural progression

**EXCEED** – psoriatic arthritis
1 year head-to-head study vs Humira®

**PREVENT** – nrAxSpA
1 year study earlier in the patient pathway in anti-TNF naïve patients

Source: clinicaltrials.gov. SURPASS: NCT03259074; EXCEED: NCT02745080; PREVENT: NCT02696031. Humira® is a registered trademark of AbbVie Inc.
Cosentyx® is well positioned in fast-growing segments of the biologics market

Global immunology¹ market
USD billion in 2016 and 2022E

<table>
<thead>
<tr>
<th>Segment</th>
<th>2016</th>
<th>2022E</th>
<th>CAGR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatology</td>
<td>56</td>
<td>65</td>
<td>2.6%</td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>14</td>
<td>16</td>
<td>6.1%</td>
</tr>
<tr>
<td>Rheumatology</td>
<td>29</td>
<td>31</td>
<td>3.0%</td>
</tr>
</tbody>
</table>

Of which USD 9bn spondyloarthritis²

US³ patient market share by indication
2016 (100% = 1,390K)

- Mature segment
  - RA
  - Gastroenterology

- Key therapies
  - Anti-TNF mAbs (incl. biosimilars)
  - JAK Inhibitors

Growth segment
- Cosentyx® target market
  - Psoriasis
  - Spondyloarthritis

1. Immunology market includes small and large molecules for rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn’s disease, ulcerative colitis and psoriasis
2. Novartis estimates based on IMS data
3. Source: DRG; Data for EUS can be found in the appendix
Increased biologics uptake in spondyloarthritis (SpA) and improved diagnoses of axial SpA should be key growth drivers

<table>
<thead>
<tr>
<th>US biologics market 2016</th>
<th>PsO</th>
<th>Spondyloarthritis</th>
<th>RA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PsA</td>
<td>AS</td>
</tr>
<tr>
<td>Prevalence</td>
<td>8400</td>
<td>1600</td>
<td>1130</td>
</tr>
<tr>
<td>Diagnosed patients</td>
<td>1700</td>
<td>1000</td>
<td>520</td>
</tr>
<tr>
<td>% diagnosed</td>
<td>20%</td>
<td>63%</td>
<td>46%</td>
</tr>
<tr>
<td>Patients treated</td>
<td>425</td>
<td>535</td>
<td>440</td>
</tr>
<tr>
<td>% treated</td>
<td>25%</td>
<td>54%</td>
<td>85%</td>
</tr>
<tr>
<td>Patients on biologics</td>
<td>164</td>
<td>100</td>
<td>84</td>
</tr>
<tr>
<td>% treated</td>
<td>39%</td>
<td>19%</td>
<td>19%</td>
</tr>
</tbody>
</table>

The number of patients eligible for biologics is similar in all 3 approved Cosentyx® indications
The US prevalence for spondyloarthritis is >50% higher than for rheumatoid arthritis
Compared to rheumatoid arthritis, spondyloarthritis is under-diagnosed and under-treated

Source: DRG Epidemiology Database 2017; IMS Health MAT Dec 16 data; Novartis Internal Analysis 1. Moderate-severe psoriasis diagnosis; 2. Systemic treated patients
Substantial scope for market expansion in Axial SpA

US market 2016
Patient numbers in thousands

### Rheumatoid arthritis
- **Prevalence**: 2500
- **Diagnosed patients**: 2200
- **Treated patients**: 1600
- **Patients on biologics**: 845

- **Prevalence**: 36%
- **Diagnosed patients**: 825
- **Treated patients**: 670
- **Patients on biologics**: 91

Of 2.2m patients, 845k (38%) are treated with biologics

Of 825k patients, 91k (11%) are treated with biologics

Source: DRG Epidemiology Database 2017; IMS Health MAT Dec 16 data; Novartis Internal Analysis
Our expectations for Cosentyx®

Psoriasis and spondyloarthritis each represent significant growth opportunities

The spondyloarthritis segment opportunity is larger than psoriasis

Under-treatment with biologics and under-diagnosis due to inadequate treatment options before Cosentyx®

• Biologics uptake is expected to double in the next decade
• Availability of effective treatment of axial SpA should drive increased diagnosis

Well differentiated in psoriatic arthritis

• Sustained long-term control of signs and symptoms (>80% ACR response at 3 years)¹⁴
• Inhibition of structural progression in >84% at 2 years⁵
• Strong data on enthesis resolution⁶,⁷,⁸
• EXCEED 1: H2H study vs. Humira® ongoing

Aiming for leadership in axial SpA

No ongoing or planned pivotal studies of anti-IL23mAbs

• Unique 4-year data:
• sustained control of signs and symptoms (80% ASAS20 and 60% ASAS40 response)⁹
• Almost 80% no radiographic progression⁹
• SURPASS: superiority H2H study vs. proposed biosimilar adalimumab allows comparative assessment of structural progression over 2 years
• PREVENT: ongoing pivotal study in nrAxSpA (earlier treatment)


Humira® is a registered trademark of AbbVie Inc.
Appendix
EU5: patient market share by indication, 2016 (100% = 966K)

- Mature segment
  - RA
  - Gastroenterology

- Growth segment
  - Psoriasis
  - Spondyloarthritis

Source: DRG/IMS
Biologics market 2016 – EU5
Patient numbers in thousands

<table>
<thead>
<tr>
<th>PsO</th>
<th>Spondyloarthritis</th>
<th>RA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PsA</td>
<td>AS</td>
</tr>
<tr>
<td>Prevalence</td>
<td>7100</td>
<td>1500</td>
</tr>
<tr>
<td>Diagnosed Patients</td>
<td>1425</td>
<td>950</td>
</tr>
<tr>
<td>% diagnosed</td>
<td>20%</td>
<td>63%</td>
</tr>
<tr>
<td>Patients eligible for biologics</td>
<td>300</td>
<td>525</td>
</tr>
<tr>
<td>% eligible</td>
<td>21%</td>
<td>55%</td>
</tr>
<tr>
<td>Patients on biologics</td>
<td>104</td>
<td>97</td>
</tr>
<tr>
<td>% treated</td>
<td>35%</td>
<td>18%</td>
</tr>
</tbody>
</table>

- In EU5, fewer psoriasis patients are treated compared to the US
- The biologics market in 3 approved indications is broadly similar
- Similar to US, the biologics uptake is lower in spondyloarthritis compared to psoriasis
- AS patients in Europe are more likely to receive biologics compared to the US, though biologic uptake for AS remains lower than in RA
- In contrast to the US, several anti-TNF mAbs are approved for nrAxSpA, resulting in modest biologics uptake in this setting, even though under-diagnosis remains a challenge

Source: DRG Epidemiology Database 2017; IMS Health MAT Dec 16 data; Novartis Internal Analysis
<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>13:30 – 14:00</td>
<td>Registration</td>
</tr>
<tr>
<td>14:00 – 14:30</td>
<td>Introduction</td>
</tr>
<tr>
<td>14:30 – 15:15</td>
<td>RTH258</td>
</tr>
<tr>
<td>15:15 – 15:45</td>
<td>AMG 334</td>
</tr>
<tr>
<td>15:45 – 16:15</td>
<td>Break</td>
</tr>
<tr>
<td>16:15 – 17:00</td>
<td>Cosentyx®</td>
</tr>
<tr>
<td><strong>17:00 – 17:30</strong></td>
<td><strong>ACZ885</strong></td>
</tr>
<tr>
<td>17:30 – 18:00</td>
<td>Q&amp;A session</td>
</tr>
<tr>
<td>18:00</td>
<td>Cocktail with management</td>
</tr>
</tbody>
</table>
**Personalized treatment for inflammatory CV risk**

CANTOS selected patients with a prior MI$^2$
- Clinically evident atherosclerosis $\rightarrow$ elevated CV risk

In addition, CANTOS selected patients with residual inflammatory risk despite optimized treatment for high risk atherosclerosis
- Patients enrolled if hsCRP$^1$$\geq$$2$mg/L $\rightarrow$ elevated CV inflammatory risk
- hsCRP$^1$: simple, inexpensive, widely available biomarker test for inflammation
- On guideline-directed optimized standard of care for high risk atherosclerosis

In CANTOS ACZ885 reduced inflammation and certain cardiovascular event rates with no effect on lipid levels

Achieving low levels of inflammatory markers $\rightarrow$ greater CV benefits accrue
- Subgroup with minimized inflammatory risk: hsCRP$^1$$<$$2$mg/L at 3 months after a single dose
- 2mg/L is a commonly used clinical threshold to identify residual inflammatory risk

---

1. hsCRP=high sensitivity C-reactive protein  
2. MI=Myocardial infarction

---

| Novartis R&D and investor day | November 13, 2017 |
Previous CV outcomes studies demonstrated importance of inflammation independent of LDL

PROVE-IT (statin treatment)

IMPROVE-IT (ezetimibe treatment)

ACZ885 (canakinumab) reduces the risk of MACE by 15% in overall studied population

150mg canakinumab administered as a quarterly injection

- Reduction in risk of MACE incl. positive trend in CV death: 15%
- Reduction in risk of MI: 24%
- Reduction in urgent revascularization procedures: 36%

Ridker et al, NEJM 2017, DOI: 10.1056/NEJMoa1707914
MACE: CANTOS primary endpoint a composite of MI, Stroke and CV death
MI: Myocardial Infarction, component of primary endpoint
Urgent revascularization procedures is a component of a statistically significant key secondary endpoint
Patients who achieved hsCRP<2.0mg/L achieved 25% relative risk reduction on MACE¹

- Achieving hsCRP below 2mg/L three months after initial injection correlates with a significant 25% RRR on MACE¹
- This effect is driven by 31% RRR in CV death and 30% RRR on MI²
- ~55% of patients

<table>
<thead>
<tr>
<th>No. at risk:</th>
<th>Follow-up years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>3182</td>
<td>3014 2853 2525 1215 200</td>
</tr>
<tr>
<td>Canakinumab</td>
<td></td>
</tr>
<tr>
<td>hsCRP &gt;= 2.0mg/L</td>
<td>2868 2724 2574 2258 1087 195</td>
</tr>
<tr>
<td>hsCRP &lt; 2.0mg/L</td>
<td>3484 3353 3214 2890 1411 243</td>
</tr>
</tbody>
</table>

Ridker et al. Lancet 2017 [in press]: [http://dx.doi.org/10.1016/S0140-6736(17)32814-3; Pooled dose analysis. 150mg arm also showed 25% RRR on MACE.](1). MACE - Major cardiovascular event (CV death, non-fatal MI, or non-fatal stroke)
2. MI – Myocardial infarction
Greater relative risk reduction in subgroup also evident for MACE + urgent revascularization

Confirmed MACE + urgent revascularization by 3-month hsCRP

![Cumulative Incidence](image)

<table>
<thead>
<tr>
<th>Placebo</th>
<th>On treatment hsCRP: &gt;=2.0mg/L</th>
<th>On treatment hsCRP: &lt;2.0mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 (ref)</td>
<td>0.91 (0.81, 1.03)</td>
<td>0.74 (0.65, 0.83)</td>
</tr>
<tr>
<td>P</td>
<td>0.14</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

- Achieving hsCRP below 2mg/L three months after initial injection correlates with a significant 26% RRR on MACE + urgent revascularization

Improved mortality also seen in subgroup: less cardiovascular and all-cause death

Incidence rates and fully adjusted hazard ratios for additional cardiovascular endpoints in CANTOS, according to on-treatment hsCRP levels at 3 months less than 2mg/L or greater than or equal to 2mg/L

<table>
<thead>
<tr>
<th>Hazard ratio</th>
<th>Cardiovascular death</th>
<th>All-cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Canakinumab 3-month hsCRP ≥ 2mg/L (N=2868)</td>
<td>0.95</td>
<td>0.69</td>
</tr>
<tr>
<td>Canakinumab 3-month hsCRP &lt; 2mg/L (N=3484)</td>
<td>0.56</td>
<td>1.05</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>P-values</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>(ref)</td>
<td>(ref)</td>
</tr>
<tr>
<td>0.95</td>
<td>0.82-1.21</td>
</tr>
<tr>
<td>0.0004</td>
<td>0.56-0.85</td>
</tr>
<tr>
<td>(ref)</td>
<td>(ref)</td>
</tr>
<tr>
<td>0.56</td>
<td>0.90-1.22</td>
</tr>
<tr>
<td>&lt;0.0001</td>
<td>0.58-0.81</td>
</tr>
</tbody>
</table>

Ridker et al, Lancet 2017 [in press]: [http://dx.doi.org/10.1016/S0140-6736(17)32814-3](http://dx.doi.org/10.1016/S0140-6736(17)32814-3); Incidence rates are calculated per 100 person-years of exposure. Covariates included in the multivariable fully adjusted data include age, gender, smoking status, hypertension, diabetes, body mass index, baseline level of hsCRP, and baseline level of LDL cholesterol.
Greater observed MACE benefits in subgroup is robust

- Consistent results across sensitivity analyses
  - Alternate subgroup analysis (e.g. median and tertile analysis) of achieved hsCRP, multivariate and dose specific analyses
  - For 150mg, HR 0.75 (95%CI 0.62-0.91, P=0.0028*) in subgroup with hsCRP <2mg/dL vs. no significant effect in subgroup for ≥2mg/L

- Results suggest simple test at 3 months after a single dose of ACZ885 can identify patients who will accrue the largest benefit from continued treatment

- Data further suggest that “lower is better” on treatment for inflammation reduction with ACZ885

- There was no statistically significant difference in incidence rates for fatal infection comparing the two ACZ885 groups defined by on-treatment levels of hsCRP at 3 months

Significant difference in absolute benefit between those who do and do not achieve hsCRP<2mg/L

Number needed to treat (NNT) of 16 to avoid one CV event in responder population

-71.4%

<table>
<thead>
<tr>
<th>CANTOS: hsCRP&lt;2mg/L @ 3mo</th>
<th>CANTOS: hsCRP≥2mg/L @ 3mo</th>
<th>CANTOS overall study population</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>56</td>
<td>24</td>
</tr>
</tbody>
</table>

MI, Stroke, coronary revascularizations, death from any cause over 5 years

Ridker et al, Lancet 2017: [http://dx.doi.org/10.1016/S0140-6736(17)32814-3](http://dx.doi.org/10.1016/S0140-6736(17)32814-3)
ACZ885 (canakinumab) generally safe and well tolerated

- Safety profile of ACZ885 was evaluated with data from 10,066 patients exposed to at least 1 dose of ACZ885, with a total of 32,663 patient-years of exposure

- ACZ885 generally safe and well tolerated. Overall incidence of AEs, SAEs, and discontinuations due to AEs similar to placebo

- Consistent with known effects of interleukin-1β inhibition significantly fewer reports of arthritis, gout, and osteoarthritis

- Cancer mortality significantly lower than with placebo

- Serious infections reported slightly more frequently as well as fatal infections with the excess compared to placebo of approximately 1 patient per 1,000 patient-years of treatment

- Management of serious infections in at risk patients should include being vigilant in early diagnosis and initiation of antibiotic treatment
In summary

- Results suggest that in the future, physicians may be able to identify patients who can achieve the greatest cardiovascular benefit from ACZ885 treatment

- 25% relative risk reduction on MACE

- 31% relative risk reduction on CV death

- 31% relative risk reduction on all cause mortality

- NNT is 16 for those who achieve hsCRP<2mg/L
Submission on track

1. Feedback from FDA and EU regulators supports moving forward with regulatory submissions for Cardiovascular risk reduction

2. Novelty of approach to reduce CV risk recognized

3. Interest in understanding relationship between hsCRP and patient response

4. Regulatory submissions planned Q4 onwards
Well defined target population for ACZ885

Incidence post MI population in US and EU5
Annual incidence, patients in thousands

1,300

Post MI incidence
1.3 million patients per year (US, EU5)

520

CANTOS study population
40% post-MI patients with high inflammatory burden
(defined as hsCRP≥2mg/L)

260

Patients who benefit most (hsCRP<2mg/l in 3 months)
~50% of patients experience greater benefit (25% RRR for MACE)
as they achieve hsCRP<2mg/L at three months after initial injection

Source: US AHA (Heart Disease & Stroke Stats 2016 update) EU5 Eurostat (# of MI Discharges), internal CANTOS data
“Residual Inflammatory Risk: Addressing the Obverse Side of the Atherosclerosis Prevention Coin”

Ridker PM. Eur Heart J 2016;37:1720-22

- **Known Cardiovascular Disease**
  - LDL 150 mg/dL (3.8 mmol/L)
  - hsCRP 4.5 mg/L
  - High Intensity Statin

- **“Residual Cholesterol Risk”**
  - LDL 110 mg/dL (2.8 mmol/L)
  - hsCRP 1.8 mg/L
  - Additional LDL reduction
  - IMPROVE-IT: Ezetimibe 6% RRR
  - FOURIER/SPIRE: PCSK9 inhibition q2 weeks 15% RRR

- **“Residual Inflammatory Risk”**
  - LDL 70 mg/dL (1.8 mmol/L)
  - hsCRP 3.8 mg/L
  - Additional inflammation reduction
  - CANTOS: ACZ885 15% RRR studied population
  - and 25% RRR in hsCRP responder group

Ridker ESC 2017
Strong value proposition a pre-requisite for uptake of a biologic treatment in a post-MI/CV risk reduction setting

**Targeting narrow, well defined population**
- ACZ885 population is well defined as post-MI and elevated inflammation (hsCRP≥2 mg/L)
- ACZ885 responder population is targeted to the patients who benefit the most (1 injection and who achieve hsCRP < 2mg/L in 3 months)

**Straightforward patient selection**
- hsCRP test is low cost and easy to perform; 1st test to identify eligible patients and 2nd test to identify responders

**Very significant magnitude of benefit in responders**
- 25% RRR in MACE (CV death, MI, stroke) in responder group
- 31% RRR in CV death alone

ACZ885 is an investigational compound for cardiovascular risk reduction and has not been approved by any regulatory or health authority for cardiovascular risk reduction.
Appendix
Dose dependent risk reduction with canakinumab in fatal lung cancer incidence of up to 77%

Cumulative incidence fatal lung cancer

<table>
<thead>
<tr>
<th></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>0.13</td>
</tr>
<tr>
<td>Canakinumab 300 mg</td>
<td>0.23</td>
<td>(0.10-0.54)</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

Follow-up years

- Advancing ACZ885 in oncology setting
- Novartis collaborating with FDA and EMA on Ph3 clinical studies; expected to start H1 2018
  - Adjuvant NSCLC
  - First-line NSCLC
  - Second-line NSCLC
CANTOS design

Spontaneous MI at least 30 days prior to randomization on standard therapies and elevated hsCRP (≥2 mg/L)

Primary endpoint: Time to first major cardiovascular event (MACE: CV death, non-fatal MI, or non-fatal stroke)

Secondary endpoints:
- **Key secondary**
  1. Time to first event of MACE or hospitalization for unstable angina requiring unplanned revascularization (UARUR)
  2. Time to new onset diabetes (NOD) among those with pre-diabetes

Other secondary endpoints
- 3. All cause mortality
- 4. Time to first occurrence of all cause mortality, non-fatal stroke, or non-fatal MI

Key exploratory endpoints: PCI/CABG, major coronary events, total vascular events, and biomarkers

**Efficacy and Safety: CANTOS Data Monitoring Committee (DMC)**

**Efficacy**
- Clinical Endpoint Committee (CEC)
- Adjudication of Death, MI, Stroke, UARUR, NOD

**Safety**
- Infection Committee (IAC) / Malignancy Committee (MAC)
- Adjudication of serious and medically significant infections and malignancies

*Loading Dose (addl. 300mg) given at week 2 post-randomization*
Background and Mode of Action
Inflammation is the hallmark of atherosclerosis, leading to MI and other CV events
## Key inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Key inclusion criteria</th>
<th>Key exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men and women of non-child-bearing potential</td>
<td></td>
</tr>
<tr>
<td>Aged ≥ 18 years</td>
<td></td>
</tr>
<tr>
<td>Documented spontaneous MI ≥30 days before randomization</td>
<td></td>
</tr>
<tr>
<td>hsCRP ≥2 mg/L</td>
<td></td>
</tr>
<tr>
<td>• Collected &lt;60 days prior to visit 2</td>
<td></td>
</tr>
<tr>
<td>• ≥28 days after qualifying MI or after any PCI performed separately</td>
<td></td>
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<tr>
<td>• On stable long-term (≥4 weeks) CV medication</td>
<td></td>
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<tr>
<td>Pregnant or nursing women</td>
<td></td>
</tr>
<tr>
<td>Any of the following concomitant conditions or diseases:</td>
<td></td>
</tr>
<tr>
<td>• Planned coronary revascularization or any major non-cardiac surgical or endoscopic procedure within the past 6 months</td>
<td></td>
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<tr>
<td>• Multi-vessel CABG surgery within the past 3 years</td>
<td></td>
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<tr>
<td>• Prior malignancy (other than basal cell skin carcinoma)</td>
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<tr>
<td>• History of ongoing, chronic or recurrent infectious disease. History or evidence of tuberculosis (active or latent) infection</td>
<td></td>
</tr>
<tr>
<td>• Nephrotic syndrome or eGFR &lt;30 mL/min/1.73 m²</td>
<td></td>
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<tr>
<td>• Suspected or proven immunocompromised state, including those with HIV infection, treatment with immunomodulatory therapy e.g. steroids with systemic effects</td>
<td></td>
</tr>
<tr>
<td>• Biologic drugs targeting the immune system (e.g., TNF blockers, anakinra, rituximab, abatacept, tocilizumab)</td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td>Event</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>13:30 – 14:00</td>
<td>Registration</td>
</tr>
<tr>
<td>14:00 – 14:30</td>
<td>Introduction</td>
</tr>
<tr>
<td>14:30 – 15:15</td>
<td>RTH258</td>
</tr>
<tr>
<td>15:15 – 15:45</td>
<td>AMG 334</td>
</tr>
<tr>
<td>15:45 – 16:15</td>
<td>Break</td>
</tr>
<tr>
<td>16:15 – 17:00</td>
<td>Cosentyx®</td>
</tr>
<tr>
<td>17:00 – 17:30</td>
<td>ACZ885</td>
</tr>
<tr>
<td><strong>17:30 – 18:00</strong></td>
<td><strong>Q&amp;A session</strong></td>
</tr>
<tr>
<td>18:00</td>
<td>Cocktail with management</td>
</tr>
</tbody>
</table>