Janssen Pulmonary Hypertension

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Global Therapeutic Area Head, Pulmonary Hypertension
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During the course of this presentation, we will discuss a number of products and compounds developed in collaboration with strategic partners, licensed from other companies, or funded by governmental or non-profit organizations. Following is an acknowledgement of those relationships:

#### Cardiovascular & Metabolism/Other

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<thead>
<tr>
<th>Product</th>
<th>Collaboration Details</th>
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<tbody>
<tr>
<td>INVOKEKAN / INVOKEKET / VOKANAMET / INVOKEKET XR</td>
<td>Fixed-dose combination licensed from Mitsubishi Tanabe Pharma Corporation; XARELTO co-developed with Bayer AG; JNJ-5111 licensed from Hammi Pharmaceutical Co., Ltd; Aproclitan licensed from Idorsia; JNJ-3093 co-developing with Bristol-Myers Squibb; Refinal assets (Achromatopsia: AAV-CNGA3, AAV-CNGB3) and (X-Linked Retinitis Pigmentosa: AAV-RPGR) licensed from MeiraGTx; Integrin therapeutics in collaboration with Morphic Therapeutics; Metabolic research discovery in collaboration with University of California San Diego.</td>
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#### Immunology

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<tr>
<td>REMICADE and SIMPONI</td>
<td>Marketed in different territories by Mitsubishi Tanabe Pharma Corporation, as well as Schering-Plough (Ireland) Company, a subsidiary of Merck &amp; Co., Inc.; TREMFYA discovered using MorphoSys AG antibody technology; VE202 licensed from Vedanta Biosciences, Inc.; JNJ-4500 (anti-NKG2D) licensed from Novo Nordisk; JNJ-4238 (PTG200) licensed from and co-developing with Protagonist Therapeutics, Inc.; JNJ-7752 (MBS2320) under option from Iisesso Ltd.; JNJ-8398 (TD-1473) co-developing with Theravance Biopharma Ireland Limited.</td>
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#### Infectious Diseases & Vaccines

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<tr>
<td>COMPLERA / EVIPLERA, ODEFSEY, SYMYTUA, PREZCOBIX / REZOLSTA</td>
<td>Fixed-dose combination products developed in collaboration with Gilead Sciences, Inc.; JULAUC developed and marketed in collaboration with ViV Healthcare Ltd.; Long-acting HIV injectable treatment regimen of rilpivirine and cabotegravir developed in collaboration with ViV Healthcare Ltd.; Pimodir licensed from Vertex Pharmaceuticals, (this project has received federal funding from BARDA, part of the U.S. Department of Health and Human Services’ Office of the Assistant Secretary of Preparedness and Response, under contract number HHSO100201500014C); Other Transaction Authority agreement No.HHSO10201700018C with BARDA, part of the U.S. Department of Health and Human Services’ Office of the Assistant Secretary for Preparedness and Response, to develop a comprehensive portfolio of therapeutics and vaccines to protect communities in the event of an influenza pandemic and other infectious disease threats.; JNJ-0535 developing in collaboration with Ichor Medical Systems; JNJ-4964 (TLR Agonist) licensed from Chia Tai Tiangning Pharmaceutical Group Co., Ltd.; JNJ-3989 licensed from Arrowhead Pharmaceuticals Inc.; Worldwide research collaboration and license with Locus Biosciences Inc., to develop, manufacture and commercialize bacteriophage products generated using Locus’s recombinant CRISPR/Cas3 Phage platform; JSC Pharmstandard manufactures and distributes SIRTURO in Russia and other countries in the region, including the Commonwealth of Independent States (CIS). Since 2005, Janssen Vaccines &amp; Prevention B.V. has been participating in the NIH-supported Integrated Preclinical/Clinical AIDS Vaccine Development (IPCAVD) program under grants AI068305, AI078529 and AI096040, in collaboration with Professor Dan Barouch at Beth Israel Deaconess Medical Center (BIDMC); Janssen’s HIV vaccine program has also received funding or support from the United States Military HIV Research Program (MRHP) at the Walter Reed Army Institute of Research (WRAIR), with the Henry M. Jackson Foundation for the Advancement of Military Medicine (HJF); the Ragon Institute; and the International AIDS Vaccine Initiative (IAVI); The phase 2b proof-of-concept efficacy study Imbokodo (HVTN 705/HPX206) for the HIV prophylactic vaccine received co-funding from two primary partners, the Bill &amp; Melinda Gates Foundation and National Institute of Allergy and Infectious Diseases (NIAID). Additional partners providing support include the U.S. Military HIV Research Program at the Walter Reed Army Institute of Research, U.S. Army Medical Materiel Development Activity, and the Ragon Institute of Massachusetts General Hospital (MGH), Massachusetts Institute of Technology (MIT) and Harvard. The study is conducted at clinical sites coordinated by the NIAID-funded HIV Vaccine Trials Network (HVTN). The South African Medical Research Council (SAMRC) is helping to implement HVTN 705/HPX206 in South Africa; License and collaboration agreements with Blink Therapeutics to leverage their MVA-BN technology with Janssen’s own ADVAC and DNA-based vaccine technologies in the development and commercialization of potential new vaccine regimens against hepatitis B virus (HBV) and the human immunodeficiency virus (HIV-1); JNJ-1623 VAC1623 (HPV vaccine) developed in collaboration with and licensed from Bavarian Nordic A/S; IPV vaccine with funding from Bill and Melinda Gates Foundation; Zika vaccine in collaboration with Beth Israel Deaconess Medical Center (Harvard Medical School); License and collaboration agreement with GSK (Glycovaxyn) for the development of ExPEC.</td>
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Strategic partnerships, collaborations and licensing arrangements

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<th>Neuroscience</th>
<th>INVEGA SUSTENNA / XEPLION / INVEGA TRINZA / TREVICTA includes technology licensed from Alkermes Pharma Ireland Limited; RISPERDAL CONSTA developed in collaboration with Alkermes, Inc; Tau vaccine developing in collaboration with AC Immune SA; JNJ-7922 (Orexin-2 antagonist) developing in collaboration with Minerva Neurosciences, Inc.</th>
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<tr>
<td>Oncology</td>
<td>BALVERSA discovered in collaboration with Astex Pharmaceuticals, Inc.; ERLEADA is licensed from The Regents of California and Memorial Sloan Kettering Cancer Center; DARZALEX licensed from Genmab A/S; YONDELIS developed in collaboration with Pharma Mar S.A.; IMBRUVICA developed in collaboration and co-marketed in the U.S. with Pharmacyclics, LLC, an AbbVie company; DACOGEN developed and commercialized in collaboration with Eisai Inc. and Otsuka Pharmaceuticals Co. Ltd.; ZYTIGA licensed from BTG International Ltd.; VELCADE developed in collaboration with Millennium: The Takeda Oncology Company; PROCRIT / EPREX licensed from Amgen Inc.; cusatuzumab licensed and developing in collaboration with Legend Biotech USA Inc., Legend Biotech Ireland Limited (“Legend”), subsidiaries of GenScript Biotech Corporation; Niraparib licensed from TESARO, Inc., an oncology-focused business within GSK; JNJ-7107 licensed from Alligator Bioscience AB; JNJ-6892 licensed from Bioer/OX Products B.V.; DUOBODY platform licensed from Genmab relates to several bispecific antibody programs; ENHANZE platform licensed from Halozyme Therapeutics, Inc.</td>
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<tr>
<td>Pulmonary Hypertension</td>
<td>UPTRAVI (selexipag), discovered and initially developed by Nippon Shinyaku, a worldwide (except for Japan) license and co-development and co-promotion agreements with Nippon Shinyaku (co-promotion in Japan) and OXUMT license agreement with Nippon Shinyaku in Japan; Strategic collaboration with Analytics 4 Life, to investigate the use of machine learning diagnostic imaging technology, to develop a single, non-invasive test to diagnose patients with all types of pulmonary hypertension.</td>
</tr>
<tr>
<td>Global Public Health</td>
<td>Janssen’s Monovalent Ebola Vaccine is developed in collaboration with Bavarian Nordic A/S, and MVA-BN-Filo® is licensed-in from Bavarian Nordic A/S. The program has benefited from funding and preclinical services from the National Institute of Allergy and Infectious Diseases (NIAID), part of NIH, NIAID support included 2 product development contracts starting in 2008 and 8 pre-clinical services contracts. This program is also receiving funding from the IM2 Joint Undertaking under EBOVAC1 (grant nr. 115854), EBOVAC2 (grant nr. 115861), EBOVAC3 (grant nr. 800176), EBMOMB (grant nr. 115850) and EBDAC (grant nr. 115847). The IM2 Joint Undertaking receives support from the European Union’s Horizon 2020 research and innovation program and the European Federation of Pharmaceutical Industries and Associations (EFPIA). Further funding for the Ebola vaccine regimen has been provided by the BARDA, within the U.S. Department of Health and Human Services’ Office of the Assistant Secretary for Preparedness and Response, under Contract Numbers HHSO100201700013C and HHSO100201500008C. The initial work on Ebola was conducted which was extended from 2002 until 2011. 2002 and 2007 via a Cooperative Research and Development Agreement (CRADA is AI-0114) between Janssen/Crucell and the Vaccine Research Center (VRC)/NIAID, part of the NIH. Janssen/Crucell have licenses to much of VRC’s Ebola IP specific for human adenovirus under the Ad26/Ad35 Ebola vaccine CRADA invention. VACE9120 (Filoivirus multivalent vaccine) developed in collaboration with Bavarian Nordic; funding: NIH Division of Microbiology and Infectious Diseases (DMID), under Contract Number HHSN272200800066C.</td>
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PH is a rare progressive disease, with various causes, and no cure

**GROUP 1**  
Pulmonary arterial hypertension (PAH)

**GROUP 2**  
PH due to left heart disease

**GROUP 3**  
PH due to lung disease and/or hypoxia

**GROUP 4**  
Chronic thromboembolic pulmonary hypertension (CTEPH)

**GROUP 5**  
PH with unclear mechanisms

**PAH facts**

- 70–120 people per million currently on treatment
- Due to lack of awareness, mean time interval between onset of symptoms and diagnosis is two years and many patients may go unidentified
- Majority of patients in advanced stage (functional class III or IV) at time of diagnosis
- Only a third of patients are receiving double or triple combination therapy
- Median survival now more than seven years with treatment
- Despite progress, one in three die within five years of diagnosis

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1. Internal estimate and quantitative Market Research, US, EU5 & JPN 2018  
Pulmonary Hypertension highlights

Growth opportunity driven by doubling treatment population through earlier diagnosis and combination treatments

1. Evaluate Pharma March 2019
2. Internal Data
3. Internal estimate and quantitative Market Research, US, EUS & JPN 2018
4. WW, world wide; CAGR, compound annual growth rate
5. PDE-5/sGC, Phosphodiesterase type 5 inhibitors/soluble guanylate cyclases; ERA, endothelin receptor antagonist; Prostaglandin I2
Our vision is to transform PH into a long-term manageable condition
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<td>Build a new pipeline of novel therapies</td>
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Significant unmet need remains in PAH and other groups of PH

Situation today in PAH

70–120 PPM*³
Patients on treatment

- 40% of patients on two drugs⁴
- 20% of patients on three drugs⁴

Future goal

>150 PPM*³

- 40% of patients on two drugs
- 50% of patients on three drugs

* People per million
3. Internal estimate and quantitative Market Research, US, EU5 & JPN 2018

Sub-optimal treatment¹

Late diagnosis/patients at advanced stage²

No cure

No approved treatments for most other PH groups

¹ Janssen Pharmaceutical Companies of Johnson & Johnson

² Janssen Pharmaceutical Companies of Johnson & Johnson

³ Janssen Pharmaceutical Companies of Johnson & Johnson

⁴ Janssen Pharmaceutical Companies of Johnson & Johnson
Our PAH medicines support patients across the spectrum of disease severity

PAH patient risk profile\textsuperscript{1,2}

Driving PH market expansion

Market growth driven by:
- Earlier diagnosis
- Earlier treatment intensification
- New indications

2018 WW Market Sales¹
$6.0B

2019 WW Market Sales¹
$7.7B

CAGR 2018–2023
5.1%

$2.1B
$2.9B
$1.0B

PDE-5s/sGC
ERAs
PGI2s

$4.1B
$2.7B
$0.8B

2023

PDE-5s/sGC, Phosphodiesterase type 5 inhibitors/soluble guanylate cyclases; ERA, endothelin receptor antagonist; Prostaglandin I2

1. Evaluate Pharma March 2019
2. Internal Data
### Realize clinical potential of current therapies

### Driving portfolio growth

<table>
<thead>
<tr>
<th>Approved products¹</th>
<th>Indications filed and potential submissions 2019–2023</th>
<th>Ongoing studies*</th>
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<tr>
<td><strong>Filed</strong></td>
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<td>OPSUMIT (macitentan)</td>
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<td>• CTEPH</td>
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<td><strong>Potential planned filings</strong></td>
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<td><strong>UPTRAVI (selexipag)</strong></td>
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<td>• Fontan-palliated subjects</td>
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<tr>
<td>• TOMORROW: Pediatric PAH</td>
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<td><strong>PORTICO: Portopulmonary hypertension (PoPH)</strong></td>
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<tr>
<td><strong>REPAIR: Right ventricular remodeling</strong></td>
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<td><strong>RUBATO: Fontan-palliated patients</strong></td>
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<td><strong>SOPRANO: PH after left ventricular assist device (LVAD) implantation</strong></td>
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<tr>
<td><strong>SERENADE: Heart failure with preserved ejection fraction and pulmonary vascular disease</strong></td>
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<tr>
<td><strong>UMBRELLA: Long-term safety data in PAH patients</strong></td>
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<tr>
<td><strong>UPTRAVI (selexipag)</strong></td>
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<td>• TRITON: Initial triple oral treatment regimen of macitentan together with selexipag and tadalafil in treatment-naive patients with PAH</td>
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<td>• Pediatric PAH: Phase 2</td>
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<td>• TRACE: Effect on the physical activity of patients with PAH. Using a wearable wrist device</td>
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<td>• PAH IV†</td>
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Note: Filings/approvals are in the US or EU, unless otherwise noted.

This information is accurate as of March 1, 2019 to the best of Johnson & Johnson’s knowledge. The Company assumes no obligation to update this information.
Realize clinical potential of current therapies

Committed to providing additional medical therapies for inoperable CTEPH

- Approx. 40,000 patients within US and Europe\(^*\)\(^1,2\)
- Can be cured with surgery but up to 50% deemed inoperable\(^3\)
- Three-year survival can be as low as ten percent if CTEPH is left untreated\(^4\)
- Currently only one licensed medical therapy for inoperable CTEPH (except Brazil)

\(^*\) Extrapolated from Kirson (2011) and Delcroix (2016)

Commitment to CTEPH

- OPSUMIT approved in Brazil
- FDA Complete Response (Jan 2019)
- EU file review ongoing
- **Selexipag**: Phase 3 study (SELECT) started
- **Macitentan + selexipag**: Combination therapy – potential to improve outcomes

\[16\%\]
Reduction in pulmonary vascular resistance (PVR) with macitentan vs. placebo (p=0.041)\(^5\)

\[34\text{ meters}\]
Improvement in six minute walking distance with macitentan vs. placebo (p=0.033)\(^5\)


TRITON: triple combination therapy in PAH building on data from SERAPHIN and GRIPHON

**Primary objective:** explore effect of initial triple combination in newly diagnosed, treatment-naïve patients

**Study design**
- Macitentan + tadalafil + selexipag
- Macitentan + tadalafil + placebo

<table>
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<tr>
<th>26 weeks</th>
<th>36 months</th>
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<tr>
<td>Risk reduction macitentan vs. placebo (HR 0.62, 95% CI 0.43-0.89)</td>
<td>38%</td>
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<tr>
<td>Risk reduction selexipag vs. placebo (HR 63, 95% CI 0.39-1.01)</td>
<td>37%</td>
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**Primary end point:** reduction in PVR

**Interim analysis:** 78 patients

Early intensification of treatment is a key driver in improving patient outcomes

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Realize clinical potential of current therapies
Realize clinical potential of current therapies

First randomized controlled trial in PoPH

Macitentan significantly improved cardiopulmonary hemodynamics: 35% reduction in pulmonary vascular resistance at week 12 for macitentan vs. placebo (p<0.0001)\(^1\)

Placebo (n=42)  
Risk category down: \(\downarrow 14\%\)

Macitentan (n=43)  
Risk category down: \(\downarrow 42\%\)

- Macitentan treated patients were almost 4 times more likely to improve their risk category, OR 3.73 [95% CI: 1.18–13.40]; (p=0.0224)\(^1,2\)
- Post-hoc analysis on hemodynamic changes with macitentan vs. placebo related to risk category for liver transplant\(^2\)

Opportunity in PoPH

- Liver transplant offers cure for patients with portal hypertension\(^3\)
- Liver transplant contraindicated in moderate to severe PoPH\(^4\)
- Macitentan can be a bridge to potentially life-saving transplantation by:
  - Improving hemodynamics and right ventricular (RV) function
  - Decreasing perioperative mortality of liver transplantation\(^5\)

1. Sitbon O, et al. OA267; Presentation at the ERS International Congress 2018
Macitentan significantly improved right ventricular function and pulmonary vascular resistance in patients with PAH\textsuperscript{1}

**REPAIR – effect of macitentan on RV remodeling**

- First multicenter study in PAH to use a primary endpoint measured by cardiac MRI\textsuperscript{1}
- Increases understanding of the effects that macitentan can have on RV remodeling and function in patients with PAH\textsuperscript{1}
- Interim analysis presented at American College of Cardiology’s 68th Annual Scientific Session
- Full study results to be presented in 2020

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1. Rosenkranz S, et al. *J Am Coll Cardiol* 2019; 73 (9 [Suppl 1])
Realize clinical potential of current therapies

Fontan-palliated patients: Meeting a growing need

Macitentan in Fontan: Rationale

- Macitentan preserves cardiac function and exercise capacity\(^6\)
- Previous randomized controlled trials in Fontan-palliated subjects treated with an endothelin receptor agonist (ERA) showed short-term improvement in exercise capacity\(^7,8\)
- Early long-term administration of macitentan may reduce the risk of morbidity events\(^6-8\)

Progress

- RUBATO Phase 3 study to assess the effect of macitentan on exercise capacity\(^†\) in Fontan-palliated subjects (ongoing)
- Study progressing well, anticipate filing in the next few years
- In discussions with health authorities around the globe

• Life-saving, surgical procedure in children with complex congenital heart defects\(^1\)

• Risk of poor long-term outcome\(^2\)

• Approx. 45 patients per million in Europe and the US*\(^3,4\)

• Estimated 1,200 new Fontan procedures annually in US\(^5\)

* Extrapolated for US and Europe from Australian and Danish registries
\(†\) As measured by peak VO\(_2\) in cardiopulmonary exercise testing
1. Gewillig M, Brown SC. Heart 2016; 102: 1081-6
Accelerate diagnosis

Driving earlier diagnosis

Primary care

Need:
Increase suspicion of PH

Advanced analytics
Electronic Medical Record algorithm for PH/PAH diagnosis

Secondary care

Need:
Faster referral to specialist center

Non- and less-invasive diagnostics/imaging/artificial intelligence (AI)

Blood and breath-based biomarkers

Novel, non-invasive diagnostic used earlier will enable:

• Faster treatment initiation with the potential to improve outcomes
• Identification of patients who would otherwise go undiagnosed

Digital platforms driving optimization of medication and adherence

Focusing on disease-modifying pathways

Building novel early stage research from the ground up

Initiation ➔ Remodeling ➔ Plexiform lesions ➔ Right ventricle failure

- HEALTHY ARTERY
- ENDOTHELIAL DYSFUNCTION
- VASCULAR REMODELING
- PLEXIFORM LESION & IN SITU THROMBOSIS
- RIGHT VENTRICULAR HYPERTROPHY

Focusing on reversing vascular remodeling by targeting cell survival signaling pathways

Key Takeaways: Transform PH into a long-term manageable condition

- **TRITON**: the promise of triple therapy in treatment-naïve patients
- **Increase patients on triple therapy** from 20% to 50%
- **CTEPH**: need new medical therapies for inoperable patients

### Realizing the clinical potential of current therapies

- **OPSUMIT (macitentan)**
  - CTEPH (in progress)
  - Fontan-palliated subjects
  - Pediatric PAH
  - Macitentan/tadalafil FDC for PAH

### Accelerating diagnosis

- Enabling patients to receive life-extending treatment, sooner
- Guidelines recommend patients should receive combination therapy earlier¹

### Building a new pipeline of novel therapies

- Reversing vascular remodeling by targeting cell survival signaling pathways

### Potential planned filings 2019–2023

- **UPTRAVI (selexipag)**
  - PAH IV
  - CTEPH

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