ViiV – R&D Strategy
Where are we heading?

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With the introduction of the INSTIs, the efficacy of first-line treatment has risen to >90%
Despite Effective ART, Serious Unmet Needs Remain

- **Do I have to take ART forever? What is the impact of chronic ART intake?**
- **Can I take drug holidays? What are the consequences?**
- **I must manage a lifetime of dealing with HIV stigma**
- **Can I ever be certain of my viral load not rebounding and transmitting my HIV?**
- **ART is improved, but there are always unforeseen side effects**
- **Is my life expectancy reduced and am I at higher risk of comorbidities?**
- **Will my immune system be fully restored?**
- **Will there ever be a cure for HIV? Are there any companies working on it?**

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We invest in R&D to benefit PLHIV

Our focus areas have the potential to change the way we treat HIV with the goal to reduce long-term toxicities and target unmet medical needs

- Small molecule ARVs
- Biologic (monoclonal antibody) ARVs
- Alternative methods of delivery (e.g. long-acting injectables)
- Simplified regimens with improved long-term outcomes
- Maturation inhibitor as possible addition to arsenal of treatment options
- Attachment inhibitor for heavily treatment-experienced patients

Ensure what we do helps PLHIV

Involve PLHIV in process

PLHIV benefit from our R&D efforts
HIV Evolution – Past and Future

1981 HIV Reported Epidemic begins with first diagnosed case

1987 First ART (AZT) Approved

1996 HAART

2006-2019 Optimization of Oral ART (2DR)

2019-2030 Long Acting ART

2019-2030 Q3M long-acting injectables

2025-2035 Long Acting ART with Reservoir Reduction

2030-2045 Functional Cure Therapies

2045+ Sterilizing Cure

Complete eradication of HIV-infected cells

Long term ART free periods (AKA remission)

Long acting ART with improved profiles that reduce reservoir size

Viral control via combination ART

Highly efficacious, safe, and well-tolerated ART in daily single tablet regimens
Discovery Strategy:

**Short-term**
- **Dolutegravir-based regimens**
  - ViiV Healthcare owned
  - New mechanism drugs to combine with dolutegravir
  - Wholly owned 2 drug regimens
  - Nuc- and booster-sparing regimens
  - “Insurance policy” for a 3 drug regimen
  - New drugs for resistant viruses

**Medium**
- **Long-acting regimens**
  - A path to a once-yearly therapy
  - Imagine a biologic regimen that could last a year “feels like remission”
  - Cabotegravir will establish long-acting depot concept
  - Combinectin is a first step to a convenient biologic regimen
  - bNAb’s show promise of long half-life

**Long-term**
- **HIV Cure**
  - One course of therapy for long-term remission
  - ViiV has a “toe in the water” with Qura
  - Unclear as to what approaches will lead to a cure
  - “Shock and Kill”; checkpoint inhibitors; reservoir micro-environment; therapeutic vaccines; bNAb; gene therapy;
  - Qura gives opportunity to participate; observe and invest when time is right

This extends our planning to 2030 and beyond
Innovative and competitive pipeline

Two Drug Regimens
- Juluca: dolutegravir/rilpivirine
dolutegravir/lamivudine FDC*

Long-acting (LA) Treatment Regimens
- cabotegravir + rilpivirine*

Current standard of care = HAART/legacy drugs

Dolutegravir-based Regimens
- Tivicay
- Triumeq

Legacy ARV Drug Portfolio
- abacavir/lamivudine, maraviroc & others

Pipeline Strategy

Prevention
- Cabotegravir LA*

New MOA
- Attachment inhibitor (fostemsavir)*
- Combinectin (GSK3732394)*‡
- Maturation inhibitor portfolio*‡
- Allosteric integrase inhibitor *‡
- Capsid inhibitor*‡

*Investigational Treatments
‡ Discovery and Early Development Programs
## Development Pipeline

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*In collaboration with Janssen

3TC, lamivudine; CAB, cabotegravir; DTG, dolutegravir; INSTI, integrase strand transfer inhibitor; LA, long-acting; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; RPV, rilpivirine; STR, single tablet regimen
Pioneering Long-Acting Injectables for HIV-1 Treatment and Prevention

- Cabotegravir (CAB) is a novel integrase inhibitor formulated as a long-acting injectable
- CAB’s innovative mode of delivery may enable monthly or less frequent dosing schedules to help overcome the barriers of medication adherence in HIV treatment and prevention
- First ARV development program with simultaneous progression of global registration programs for both treatment and prevention indications
Fostemsavir: a life-saving investigational medicine for patients with few or no treatment options left

First-in-class – unique mechanism that blocks initial CD4 binding

No cross-resistance to other antiretrovirals

FDA breakthrough therapy designation US regulatory filing planned for 2019

Demonstrated efficacy for heavily treatment-experienced patients – BRIGHTE study showed 54% of patients achieved virologic suppression at 48 weeks and had continued increase in CD4+ t-cell counts

Maturation Inhibitors (GSK3640254)

Maturation inhibitors block protein processing late in the viral replication cycle

ViiV is progressing oral and long-acting MI programs

Oral program to include single entity and combination product with DTG

Targeting frequency of every two months or less

Long acting MI could serve as a partner for CAB LA
Vision for Biologics

Combinectin

- Three modes of action in a single injectable\(^1\)
- Broad-spectrum biologic agent
- Capable of once-monthly self-administered, subcutaneous dosing
- All-in-one regimen, or as a partner for CAB, or another LA agent

bNAbs

- Long acting\(^2\)
- Naturally long half-life (2-3 weeks) and modifiable
- Role in remission and cure\(^3\)
- Potential for targeting HIV reservoir
- Partner for CAB or another LA agent

„Today we treat the virus,
    ....tomorrow we will treat the host!“
HIV, immune activation, and inflammation
**Novel therapeutic strategies?**

- **HIV INFECTION**
  - Early Antiretroviral Treatment
  - Restore Immune Function
  - Prevent AIDS
  - Improve Quality of Life
  - Prolong Life

- **INFLAMMATION & CHRONIC IMMUNE ACTIVATION**
  - Therapeutic Options Targeting Host Factors/Responses?
  - Efficient Immune Function? Low HIV Reservoirs?
  - Remission / Cure?
Bridging from ART to Cure

Can future innovations in ART deliver incremental gains before cure regimens become a reality?

Can incremental innovation on curative therapies represent value to patients as stand alone therapies?
We aim to reduce the HIV reservoir and/or improve host immunity to achieve ART-free duration >2 years

Upside: May lessen NCD risk
HIV Cure Product Vision

Requirements to Deliver for Patients:
- Extra benefit beyond classic ART
- Reservoir reduction capacity and/or enhancement of anti-HIV immune responses
- Acceptable safety/tolerability profile
- Viral suppression comparable to SOC
- Long-acting (durability >2 years) without drug on board
- No viral transmission in the absence of ART
- Cost? Access?

- Initial treatment course with cure regimen in combination with long acting ART
- Follow-up treatments every 2-5 yrs
- Tolerability no worse than flu like symptoms at each treatment
Building the HIV Cure Regimen: Extending the Long Acting Portfolio

Example Regimens
- CARLA
- CAB+ bnAb(s)
- bnAb(s)+ SMACm
- bnAb(s)+ SMACm+ TherVax

Intervention Interval
- Q1M/Q2M
- Q3M
- Q1yr
- Q2-5yr

Safety
- SOC
- Flu-like symptoms
- Flu-like symptoms

Market Timeline
- Filed 2027+
- 2030+
- 2035+
SMACm: A More Effective Latency Reversal Strategy

- SMACm directly reactivate latent SIV and HIV *in vivo*
- Limited immunologic impacts
- Contrast to indirect, inconsistent, inflammatory TLR7 agonist approach
- Potential selective killing of HIV-infected cells
- Novel lead molecules discovered at Qura

SMACm are a refined LRA strategy with potential to reduce the reservoir
N6LS/VRC07: bnAb with Potent Antiviral Activity and Potential Reservoir Reduction Properties

**Neutralization**
(Direct acting antiviral)

- Bind HIV envelope and prevent virus entry into target cells

**Enhanced Host Immune Response**
(Clearance of infected cells)

- Antigen binding
- Fc region binds to Fc Receptors on innate cells
- bnAb+ virus can form complexes that are presented to the host immune system and may induce:
  - Antibody responses
  - T cell responses
- bnAbs can facilitate clearance of infected cells

- N6LS demonstrates superior antiviral potency/clade coverage compared to other bnAbs
Radboud Collaboration to Identify HIV Patient Specific NCD Pathways and Biomarkers

Currently Available
- Environmental data
- Psychiatric data
- (Longitudinal) clinical data
- Immunophenotyping
- Functional immunology (PBMCs cytokine production)
- Platelet function
- Soluble markers (inflammation, microbial translocation, coagulation)
- Metabolomics

In Progress
- Genetics
- Microbiome
- Platelet RNA/mtDNA
- Carotid thickness and pulse wave velocity
- Fibroscan

Future Capabilities
- HIV reservoir
- Transcriptomics
- Proteomics (O-LINK)

200HIV -> 2000HIV