Primary Analysis of ASCENT
Phase 1/2a study to assess the safety/tolerability and immunogenicity of 2 different heterologous vaccine regimens


*Sr. HIV Biomarker Lead, **Study Statistician

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Disclosure

I have the following conflicts of interest to declare:

- I am an employee of Janssen Vaccines & Prevention B.V., a pharmaceutical company of Johnson & Johnson

- I hold equity shares in Johnson & Johnson
Our goal

A prophylactic HIV vaccine that protects against the globally relevant strains of HIV-1

Heterologous vaccine regimen using Ad26 viral vectors expressing mosaic HIV antigens, and soluble trimeric gp140 envelope proteins
Clinical development plan

NHP #13-19
Pre-clinical study

Ph2a APPROACH N=393
FIH Ad26.Mos.HIV and heterologous regimens

Ph2a TRAVERSE N=198
3-valent Ad26 vs 4-valent Ad26

Ph2b IMBOKODO N=2,637

Ph2a ASCENT N=152
Clade C+Mos gp140 vs Clade C gp140 alone

Ph3 MOSAICO N=3,800

|------|------|------|------|------|------|------|------|------|------|

Clade C+Mos gp140 vs Clade C gp140 alone
A randomized, parallel-group, placebo-controlled, double-blind Phase 1/2a study in healthy HIV uninfected adults to assess the safety/tolerability and immunogenicity of 2 different heterologous vaccine regimens
Expanding breadth & magnitude of responses

- Ad26.Mos.HIV
  - Ad26.Mos2.Gag-Pol
  - Ad26.Mos1.Env
  - Soluble gp140 + alum
    - Clade C gp140 – 250 mcg

- Ad26.Mos4.HIV
  - Ad26.Mos2.Gag-Pol
  - Ad26.Mos1.Env
  - Ad26.Mos2S.Env
  - Soluble gp140 + alum
    - Clade C gp140 – 250 mcg
TRAVERSE Immuneogenicity
Significant improvement across clades of humoral and cellular assays

GMR (95% CI) of 4-valent over 3-valent

Total IgG ELISA
- Clade A
- Clade B
- Clade C
- Consensus C
- Mosaic1

IgG Clade C ELISA
- IgG 1
- IgG 3

ADCP
- Clade A
- Clade B
- Clade C
- Consensus C
- Mosaic1
Preparing for Phase 3 efficacy trials

- Ad26.Mos4.HIV and Clade C gp140 induced **superior magnitude** cellular and humoral immunity

- Bivalent Ad26-vectored Mosaic Gag-Pol and Env antigens **increase breadth** of immune responses

**Expand global coverage**
Aiming to expand the scope of global coverage

- Ad26.Mos2.Gag-Pol
- Ad26.Mos1.Env
- Soluble gp140 + Alum
  - Clade C gp140 - 250mcg

- Ad26.Mos2.Gag-Pol
- Ad26.Mos1.Env
- Ad26.Mos2S.Env
- Soluble gp140 + Alum
  - Clade C gp140 - 250mcg

- Ad26.Mos2.Gag-Pol
- Ad26.Mos1.Env
- Ad26.Mos2S.Env
- Soluble gp140 + Alum
  - Clade C gp140 - 250mcg
  - Mosaic1 gp140 - 125mcg
A randomized, parallel-group, placebo-controlled, double-blind Phase 1/2a study in healthy HIV uninfected adults to assess the safety/tolerability and immunogenicity of 2 different heterologous vaccine regimens
### ASCENT: study design

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Vacc 1, 2 (wk 0, wk12)</th>
<th>Vacc 3, 4 (wk 24, wk 48)</th>
<th>Follow up (wk 72)</th>
<th>Long term extension (up to 3.5 years post last vx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>100</td>
<td>Ad26.Mos4.HIV</td>
<td>Ad26.Mos4.HIV + Clade C gp140 + Mosaic1 gp140</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>Placebo</td>
<td>Placebo</td>
<td></td>
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</tbody>
</table>
Study Overview

**Primary Objectives**
To assess safety/tolerability of the 2 different vaccine regimens
To compare Env binding antibody responses of the 2 different vaccine regimens

**Secondary:** to compare cellular and other humoral immune responses of the 2 different vaccine regimens

**Population**
Healthy adults, 18-50 years
N: 152 (actual)

Sex:
- Male: 62
- Female: 90

Locations:
- USA: 107
- Kenya: 5
- Rwanda: 40

Data from: Janssen Infectious Diseases & Vaccines
Safety

Both vaccine regimens were well tolerated
Through Week 52, 4 weeks post final vaccination

No related SAEs, deaths or HIV infections
No study pausing rules met
  • Reactogenicity profile similar between groups and similar to previous experience
  • Most frequent reported solicited adverse events were injection site pain, fatigue, headache and myalgia
  • Most unsolicited events were mild and moderate
  • No differences between active groups after third or fourth vaccinations
Immunogenicity

No interference in Clade C gp140 binding antibody response

<table>
<thead>
<tr>
<th></th>
<th>Pooled Baseline</th>
<th>Bivalent</th>
<th>Clade C</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td>Responders/Total</td>
<td>90/90</td>
<td>82/82</td>
<td>20/20</td>
<td>2/25</td>
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<tr>
<td>ELISA titre</td>
<td></td>
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<tr>
<td></td>
<td>10^2</td>
<td>10^4</td>
<td>10^5</td>
<td>10^2</td>
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<tr>
<td>Responders</td>
<td>90/90</td>
<td>82/82</td>
<td>20/20</td>
<td>2/25</td>
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<tr>
<td>Non-responders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responder</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
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</tbody>
</table>

Legend:
- Pooled Baseline
- Bivalent Responder
- Clade C Responder
- Placebo Responder
- Non-responder

LLOQ

Responders/Total:
- Pooled Baseline: 90/90
- Bivalent: 82/82
- Clade C: 20/20
- Placebo: 2/25
Immunogenicity

Increase in Cross Clade binding antibody responses:
Pooled TRAVERSE and ASCENT analysis

<table>
<thead>
<tr>
<th>Clade</th>
<th>Janssen ELISA</th>
<th>Bivalent gp140 N</th>
<th>GM</th>
<th>Clade C gp140 N</th>
<th>GM</th>
<th>GMR (95% CI)</th>
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<tbody>
<tr>
<td>Clade A</td>
<td>82</td>
<td>139725</td>
<td>110</td>
<td>127530</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>(92UG037.1)</td>
<td></td>
<td>(0.9,1.4)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Clade B</td>
<td>81</td>
<td>133424</td>
<td>110</td>
<td>62235</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>(1990a)</td>
<td></td>
<td>(1.7,2.7)</td>
<td></td>
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<tr>
<td>Clade C</td>
<td>82</td>
<td>237501</td>
<td>110</td>
<td>144622</td>
<td>1.6</td>
<td></td>
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<tr>
<td>(Con C)</td>
<td></td>
<td>(1.3,2)</td>
<td></td>
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<tr>
<td>Clade C</td>
<td>82</td>
<td>110084</td>
<td>110</td>
<td>112077</td>
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<tr>
<td>(ZA)</td>
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<td>(0.8,1.3)</td>
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</tr>
<tr>
<td>Mos1</td>
<td>82</td>
<td>137520</td>
<td>108</td>
<td>95400</td>
<td>1.4</td>
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<tr>
<td></td>
<td></td>
<td>(1.1,1.9)</td>
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</table>

Geometric Mean Ratio (95% CI) at Week 52 of Bivalent / Clade C gp140
**Immunogenicity**

High rates of IgG3 induction are maintained: 1086C gp140

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Responders/Total: 88/90, 79/82, 18/20, 14/17, 0/25, 0/23
Immunogenicity

Humoral responses cover global Env diversity:
BAMA Total IgG magnitude & breadth

9 gp140 antigens
16 V1V2 antigens

Global breadth across predefined* antigen panels

*N Yates et al, JVI 2018
Immunogenicity
Humoral responses cover global Env diversity:
BAMA Total IgG magnitude & breadth

Global breadth across predefined* 16 V1V2 and 16 gp120 & gp140 antigen panel

*N Yates et al, JVI 2018
Immunogenicity

Functional antibody dependent cellular phagocytosis response: Clade C gp140

[Graph showing phagocytosis score (PS) across different groups: Pooled Baseline, Bivalent, Clade C, Placebo. Responders/Total: Pooled Baseline 90/90, Bivalent 82/82, Clade C 19/20, Placebo 2/25. LOD (Limit of Detection) indicated.]
Immunogenicity

Broad ADCP responses are induced post 3rd vaccination

Clade A

Clade B

Consensus C

Mosaic
Immunogenicity

Env specific cellular responses are consistently induced: IFNγ ELISpot

Mosaic 1 Env

Mosaic 2 Env

Responders/Total: 76/89 69/82 19/21 16/17 1/25 3/23
Immunogenicity

Env specific cellular response are consistently induced: PTE Env ELISpot

Responders/Total:
- Pooled Baseline: 73/89
- Bivalent 3rd: 72/82
- Bivalent 4th: 19/21
- Clade C 3rd: 14/17
- Clade C 4th: 0/25
- Placebo 3rd: 0/25
- Placebo 4th: 1/23

Threshold
Immunogenicity

Increased cellular response: IFNγ and/or IL-2 Mos1 Env vaccine-matched peptides

**CD4 gp120**

<table>
<thead>
<tr>
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<th>3rd</th>
<th>4th</th>
<th>3rd</th>
<th>4th</th>
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<tbody>
<tr>
<td>Bivalent</td>
<td>68/84</td>
<td>52/71</td>
<td>10/20</td>
<td>8/14</td>
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<tr>
<td>Placebo</td>
<td>0/24</td>
<td>0/21</td>
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**CD8 gp120**

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>Bivalent</td>
<td>21/87</td>
<td>17/79</td>
<td>2/19</td>
<td>2/17</td>
</tr>
<tr>
<td>Placebo</td>
<td>0/24</td>
<td>0/23</td>
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</tr>
</tbody>
</table>
Immunogenicity

Clade C cellular responses maintained: IFNγ and/or IL-2 to Clade C Env vaccine-matched peptides

CD4 gp120

% of CD4+ T cells

≤ ≤

3rd 4th 3rd 4th 3rd 4th

Bivalent 40/84 31/71 8/20 6/14 0/24 0/21

Clade C

Placebo

Responders/ Total: 8/20 6/14 0/24 0/21

CD8 gp120

% of CD8+ T cells

≤ ≤

3rd 4th 3rd 4th 3rd 4th

Bivalent 8/87 8/79 3/19 5/17 0/24 0/23

Clade C

Placebo

Responders/ Total: 8/87 8/79 3/19 5/17 0/24 0/23

Legend

- Bivalent Responder
- Clade C Responder
- Placebo Responder
- Non-responder

[Graphs showing distribution of CD4 and CD8 T cells for Clade C and Placebo groups]
Conclusions
ASCENT, Week 52

Safety: both vaccines are well tolerated

Global breadth: bivalent regimen is globally relevant and induces broader immune responses

Cellular response: increase in Mosaic Env-specific CD4 T cells

Clade C responses: not affected by improved clade B and Mosaic specific immune responses

Ad26.Mos4.HIV and bivalent gp140 regimen selected for phase 3 efficacy study: MOSAICO
MOSAICO - Study design

3,800 participants; 1:1 randomization (stratified by site)

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Vacc 1</th>
<th>Vacc 2</th>
<th>Vacc 3</th>
<th>Vacc 4</th>
<th>Follow up</th>
<th>Primary analysis</th>
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<tbody>
<tr>
<td>2</td>
<td>1,900</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
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</tbody>
</table>

Follow-up

HIV-1 negative: ≥24 m after 3rd vaccination

HIV-1 positive: 6 m after diagnosis
### External Collaborators & Partners

<table>
<thead>
<tr>
<th>Institution</th>
<th>Members</th>
</tr>
</thead>
</table>
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Katy Stephenson    
Joseph Nkolola |
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Nina Russell    
Peggy Johnston    
Lut Van Damme |
| **DAAIDS, NIAID**                 | Carl Dieffenbach    
Dale Hu    
Mary Marovich    
Michael Pensiero    
Tina Tong    
Edith Swann    
Julia Hutter |
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| **HVTN**                          | Larry Corey    
Nicole Frahm    
Peter Gilbert    
Glenda Gray    
Jim Kublin    
Julie McElrath    
Georgia Tomaras    
Stephen De Rosa |
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Bruce Walker |
| **USAMMDA**                       | Elisabeth Heger |

...and their teams
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Hanneke Schuitemaker
Stefan Thoelen

...and their teams

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