Sabin-IPV clinical studies

Wilfried Bakker
12th OPV & IPV manufacturers consultation
WHO, Geneva
10 October 2013
Development of sIPV at Intravacc

- New Dutch governmental (MoH) institute
- Former Vaccinology Unit of RIVM (and NVI)
- Mission: Promoting public health by developing vaccines from the laboratory to clinical study in man
Development of sIPV at Intravacc

- Upon request of WHO, Intravacc has developed a novel IPV based on the attenuated polioviruses Sabin-strains (currently used for OPV): sIPV

- A scale-down model of IPV production was used to set-up the process

- Produced (including QC-testing) at industrial scale under cGMP:
  - 3 Master Seed Lots
  - 3 Working Seed Lots
  - 6 Monovalent Pools
  - 2 Pre-Clinical Final Lots (high dose: plain & adjuvanted)
  - 6 Clinical Final Lots (3 doses: plain & adjuvanted)

- Phase I clinical trial in adults in Poland (EU) and Cuba
- Phase I/IIa clinical trial in infants in Poland (EU)

- Technology transfer to manufacturers in developing countries
**Sabin-IPV development strategy**

**Salk-IPV**
- Routine GMP Production
- MVDA for Process understanding
- Lab-scale equivalent USP & DSP

**Sabin-IPV**
- Phase I Clinical lot Production (GMP)
- Lab-scale equivalent used to set new specs.

**Salk-IPV & Sabin-IPV**
- Scale-up to production-scale
- Technology Transfer
- Study improvements At lab-scale & optimize

Bakker et al 2011 Vaccine
Immunogenicity: wt-polio Virus neutralization titer

Wild-type Virus Neutralisation Titer (2log)

DU/shd

Type 1

Salk IPV
Sabin IPV
Sabin IPV + Al(OH)₃

Type 2

Type 3

Westdijk et al 2011 Vaccine
Westdijk et al 2013 Vaccine
Institute for Translational Vaccinology

Compare the upper wt-polio VNT limits difference type 1 and 2

Please note:
VNT of sIPV type 2 is $6 \log_2$-cycles (= 64 x) higher than type 1 (in rats)

→ In contrast to earlier findings by others:
    upon using the appropriate dosage,
sIPV type 2 is extremely immunogenic !!!

sIPV reference standard is needed
Stability of sIPV final lot (high-dose)

D-antigen (and rat potency data) show that sIPV final lot plain and adjuvanted are stable for at least 30 months.
Sabin-IPV vaccine formulation considerations:

1. Neutralizing antibody titer should be equal or higher than that induced by the international (Salk-IPV) reference.

2. At higher D-antigen doses a plateau in neutralizing antibody level is reached.

<table>
<thead>
<tr>
<th>Type</th>
<th>Plain formulation (DU / single human dose)</th>
<th>Al(OH)₃ formulation (DU / single human dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High</td>
<td>Target</td>
</tr>
<tr>
<td>Type 1</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Type 2</td>
<td>32</td>
<td>16</td>
</tr>
<tr>
<td>Type 3</td>
<td>64</td>
<td>32</td>
</tr>
</tbody>
</table>

For reference: plain Salk-IPV formulation is (type 1 – 2 – 3): 40 – 8 – 32 DU/shd.
## Sabin-IPV clinical studies: Phase I/II

<table>
<thead>
<tr>
<th>Age group</th>
<th>Arm</th>
<th>Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult</td>
<td>High dose Sabin-IPV</td>
<td>0, 2</td>
</tr>
<tr>
<td>(19-49 yrs)</td>
<td>High dose Adjuvanted Sabin-IPV with IPV</td>
<td>4, 6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10, 12, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50</td>
</tr>
<tr>
<td>15/arm</td>
<td>DSMB</td>
<td></td>
</tr>
<tr>
<td>Infants</td>
<td>Low dose Sabin-IPV</td>
<td>0, 2</td>
</tr>
<tr>
<td>(2 mos)</td>
<td>Low dose Adjuvanted sIPV</td>
<td>4, 6</td>
</tr>
<tr>
<td>Reference:</td>
<td>low IPV (Salk)</td>
<td></td>
</tr>
<tr>
<td>20/arm</td>
<td>Middle dose Sabin-IPV</td>
<td>0, 2</td>
</tr>
<tr>
<td></td>
<td>Middle dose Adjuvanted sIPV</td>
<td>4, 6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10, 12, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50</td>
</tr>
<tr>
<td></td>
<td>High dose Sabin-IPV</td>
<td>0, 2</td>
</tr>
<tr>
<td></td>
<td>High dose Adjuvanted sIPV</td>
<td>4, 6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10, 12, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50</td>
</tr>
<tr>
<td></td>
<td>DSMB</td>
<td></td>
</tr>
</tbody>
</table>
Sabin-IPV phase I/II trial (adults & infants)

- Two countries selected: Poland (EU) and Cuba

  > Poland:
    - Adult trial: completed
    - Infant trial: all visits completed. Sera have been analyzed. Data analysis in progress, preliminary data available.

  > Cuba:
    - Adult trial: completed
Clinical phase I study in healthy adults

• Three groups (n=15/group):
  • Salk-IPV (40-8-32 DU)
  • high dose Sabin-IPV (20-32-64 DU)
  • high dose Sabin-PV adjuvanted (10-16-32 DU)

• Healthy male adults
• Single vaccination (=booster dose), previous vaccinations with OPV
• Safety evaluation of solicited adverse events during 4 days and severe adverse events during 6 months
• Immunogenicity: virus neutralizing titers in blood before and 4 weeks after vaccination
  • Assay performed by CDC (US)
Safety in adults: adverse reactions (example)

- Comparable in all groups
- Well-tolerated

- At least one reaction
  - Sabin-IPV
  - Adj. Sabin-IPV
  - cIPV

- At least one local reaction

- At least one systemic reaction

Verdijk et al 2013 Vaccine
Seroprevalence before and after vaccination (adults)

- Reverse cumulative distribution curves

VNT against Mahoney (representative example)

Verdijk et al 2013 Vaccine
Seroprevalence before and after vaccination (adults)

Type 2 example

Sabin-2

MEF-1

Verdijk et al 2013 Vaccine
Conclusion adults study

• High dose Sabin-IPV and high dose adjuvanted Sabin-IPV are:
  > Well-tolerated
  > Equally immunogenic as booster vaccine compared with cIPV (in OPV immunized subjects)
## Sabin-IPV clinical studies: Phase I/II

<table>
<thead>
<tr>
<th>Age group</th>
<th>Arm</th>
<th>Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult (19-49 yrs)</td>
<td>High dose Sabin-IPV</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>High dose Adjuvanted Sabin-IPV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>wIPV</td>
<td></td>
</tr>
<tr>
<td>15/arm</td>
<td>DSMB</td>
<td></td>
</tr>
<tr>
<td>Infants (2 mos)</td>
<td>Low dose: -Sabin-IPV</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>-Adjuvanted sIPV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>wIPV (Salk)</td>
<td></td>
</tr>
<tr>
<td>20/arm</td>
<td>Middle dose: -Sabin-IPV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-Adjuvanted sIPV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High dose: -Sabin-IPV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-Adjuvanted sIPV</td>
<td></td>
</tr>
</tbody>
</table>

- IPV
- Blood collection

*Institute for Translational Vaccinology*

Verdijk et al 2011 ERV
Phase I-IIa clinical trial: study design

- **Controlled, double blind, randomized dose-escalation trial**
- **Primary objective: Safety**
  - Is the vaccine well-tolerated?
    - Solicited adverse events following immunization (diary)
    - SAE during six months (Follow-up call)
- **Secondary objective: Immunogenicity:**
  - Does the vaccine induce seroprotection?
  - Did we select the right D-antigen-dose?
  - Does ALOH₃ have a (2-fold) adjuvating effect?
    - Seroconversion rate for polio neutralizing antibodies (wild and Sabin poliovirus strains)
    - GMT
Seroprotection rate infants study

<table>
<thead>
<tr>
<th>Groups</th>
<th>Sabin-1</th>
<th>Sabin-2</th>
<th>Sabin-3</th>
<th>Mahoney</th>
<th>MEF-1</th>
<th>Saukett</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose Adj. sIPV</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>95%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Low dose sIPV</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Middle dose Adj. sIPV</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Middle dose sIPV</td>
<td>95%*</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>High dose Adj. sIPV</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>High dose sIPV</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Salk-IPV</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

*One subject had very high prevaccination titer (>10.5) and intermediate post-vaccination titer (6.83 log2 titer)
WHAT IS THE OPTIMUM FORMULATION?
Preliminary conclusions infants study

• Sabin-IPV and adjuvanted Sabin-IPV are well-tolerated

• Sabin-IPV and adjuvanted Sabin-IPV are immunogenic in infants

• Titers induced by Sabin-IPV are more effective in neutralizing the Sabin-strains

• There is an adjuvating effect of AIOH$_3$
  > However, it appears less then 2-fold (preliminary)
Sabin-IPV development strategy

<table>
<thead>
<tr>
<th>Salk-IPV</th>
<th>Sabin-IPV</th>
<th>Salk-IPV &amp; Sabin-IPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine GMP Production</td>
<td>Phase I Clinical lot Production (GMP)</td>
<td>Scale-up to production-scale</td>
</tr>
<tr>
<td>MVDA for Process understanding</td>
<td>Lab-scale equivalent used to set new specs.</td>
<td>Technology Transfer</td>
</tr>
<tr>
<td>Lab-scale equivalent USP &amp; DSP</td>
<td>Study improvements At lab-scale &amp; optimize</td>
<td></td>
</tr>
</tbody>
</table>

Bakker et al 2011 Vaccine
Sabin-IPV technology transfer

Workshop on “Sabin IPV: Challenges and Benefits”
28-30 June 2010
Selected Partners

2010
12 Interested Parties
- Panacea Biotec
- LG Life Sciences

2011
11 Interested Parties
- China National Biotec Group

2012
8 Interested Parties
- Birmex
- Sinovac
Preliminary Economics

• For conventional IPV approx. 2.5 mL bioreactor volume is required to make one dose (based on literature)

• For current Sabin-IPV manufacturing to be transferred to Technology Transfer partners (low dose formulation and optimized process, within currently studied ranges) this is approx. 2.5 – 3.0 mL bioreactor volume per dose
Preliminary Economics

- Future fully optimized Sabin-IPV manufacturing (using Animal-Component Free media, low dose formulation and fully optimized process) this is approx. 0.5 – 1.0 mL bioreactor volume per dose (feasibility shown)

Thomassen et al 2013 Vaccine, accepted
Acknowledgements & Questions

This work was supported by:

using funds provided by a grant from:

VNT analysis human studies by CDC

Thanks for their contributions:

Yvonne Thomassen – Process Development
Janny Westdijk – Formulation & Assay Dev.
Bernard Metz – Inactivation Studies
Eric van Gerven – Facilities / Validation
Nico van den Heuvel / Eelco Sleeman – Production
Fred van Nimwegen – QC
Peter van ‘t Veld – QA
Lars Sundermann / Nicole Booden – QP
Pauline Verdijk – Clinical Studies
Monique van Oijen – Registration
Ahd Hamidi – Technology Transfer
Wilfried Bakker – Project management

And many other colleagues