Advancements in Novel Vaccines against Hepatitis E & Cervical Cancer at Innovax

Xiamen Innovax Biotech Co. Ltd.

James Wai Kuo Shih
October 31, 2018
DCVMN 19th Annual General Meeting, Kunming, China
1. Hecolin® -- World's only Vaccine against Hepatitis E

2. Cecolin® -- World's Brand New HPV Vaccine
Hecolin® --
World's only Vaccine against Hepatitis E
Hepatitis E — A Global Health Issue

In highly endemic area, big outbreak with thousands cases appears periodically.

- 2012.08-2013.09, South Sudan, 12,386 cases, 225 deaths.
- 2004, Darfur, Sudan, 2,621 cases, 45 deaths.
- 1955-1956, New Delhi, India, 97,000 cases.
- 1978-1982, Kashmir, India, 52,000 cases, 1,700 deaths.
- 1986-1988, Xinjiang, China, 119,280 cases, 707 deaths (414 pregnant).
- 1955-1956, Kyrgyz Republic, Former USSR, 10,812 cases.
- 1978-1982, Kashmir, India, 52,000 cases, 1,700 deaths.
- 1976-1977, Mandalay City, Burma, 20,000 cases.
- 1973-1974, Kathmandu Valley, Nepal, 10,000 cases, 30 deaths were pregnant.
- 2014.4-, Morang District, Nepal, >6000 cases.
Hepatitis E — Recent Outbreaks in Africa
(Oct. 5\textsuperscript{th}, 2018)

- **Nigeria**: In 2017-2018: 1651 (182)
- **Congo**: In 2006: 341 (13)
- **Sudan**: In 2004: 2621 (45)
  - In 2010-2011: 39 (11)
  - In 2014: 712 (3)
  - In 2018: 129 (16)
- **South Sudan**: In 2012-2013: 12386 (225)
  - In 2018: 147 (19)
- **Chad**: In 2004: 1442 (46)
  - In 2016-2018: 1874 (98)
- **Ethiopia**: In 2014: 367 (13)
- **Kenya**: In 2012: 349 (10)
- **Uganda**: In 2007-2009: 10356 (30)
  - In 2013-2014: 656 (19)
- **Niger**: In 2017-2018: 2078 (439)
- **Central Africa**: In 2002: 715
  - In 2004-2005: 411
  - In 2018: 31 (29)
- **Namibia**: In 2017-2018: 2554 (395)
Hecolin® -- World's only Vaccine against Hepatitis E

- **1998**: HEV vaccine program initiated by NIDVD
- **2003**: Pre-clinical study finished and IND submitted
- **2004-2006**: Ph1 & Ph2 CT
- **2007-2009**: Ph3 CT completed and NDA application submitted
- **~2019**: Launched in China

- WHO Prequalification
- GMP Certificate
- New Drug Certificate

Hecolin® -- World's only Vaccine against Hepatitis E
Serotype

Expression system

Target population

Presentation

Shelf-life

Schedule

Formulation

- 30µg HEV239 VLPs, arising from genotype 1
- *Escherichia coli* expressed VLP vaccine
- ages ≥ 16 yr
- 0.5ml of suspension per dose in pre-filled syringe
- 2-8°C for 36 months
- 0, 1, 6 m
- Adjuvanted with Alum; Thiomersal as preservative.
### Registration of Hecolin®

**Designed capacity**
- 5 million doses/year

**Regular stock**
- ≥ 100,000 doses

<table>
<thead>
<tr>
<th>Country</th>
<th>Registration status</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>Approved in 2012</td>
</tr>
<tr>
<td>Pakistan</td>
<td>Technical review completed; GMP inspection finished smoothly in September 2018</td>
</tr>
<tr>
<td>Thailand</td>
<td>GMP approved; Sample testing completed in May 2018; Under technical evaluation</td>
</tr>
<tr>
<td>India</td>
<td>Under technical evaluation</td>
</tr>
<tr>
<td>USA</td>
<td>Pre-IND dossier finished; IND dossier under preparation, to be submitted in 2018</td>
</tr>
<tr>
<td>Indonesia</td>
<td>Dossier under preparation, to be submitted in 2018</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>Dossier under preparation, to be submitted in 2018</td>
</tr>
<tr>
<td>WHO PQ</td>
<td>Dossier under preparation, to be submitted in 2019</td>
</tr>
</tbody>
</table>
# Major Phase IV Clinical Studies of Hecolin®

<table>
<thead>
<tr>
<th>Subject</th>
<th>Conclusion</th>
</tr>
</thead>
</table>
| To evaluate the safety and immunogenicity in elderly                   | - The vaccine is safe and immunogenic in test group (age >65yr) to control group (age 18-65)  
- The vaccine is well-tolerated:  
  - no vaccine associated SAE was observed;  
  - The rate of solicited AE in test group (age >65yr) has no statistical significant difference with control group (age 18-65);  
  - The rate of unsolicited AE in test group (age >65yr) has no statistical significant difference with control group (age 18-65). |
| To co-administrate Hecolin® with Hepatitis B vaccine.                 | - Co-administration was immunogenic and generally well tolerated.  
- The study results support the co-administration of Hepatitis E vaccine with Hepatitis B vaccine in healthy adults aged above 18 years old |
| To evaluate the immunogenicity and safety in the chronic Hepatitis B patients | - The hepatitis E vaccine is well tolerated and immunogenic in the CHB patients aged 30 and older.                                                                                                     |
| To evaluate the immunogenicity and safety with accelerated vaccination schedule | - An accelerated schedule is safe and provides protective antibody in a shorter time compared to the routine schedule.  
- The accelerated schedule should be recommended to adults who are hurried travelers to a Hepatitis E endemic area or during a Hepatitis E outbreak setting. |
WHO Recommendation (TRS) and Standard

- May 2017, Geneva
  First working group meeting

- Nov. 2017
  First version of TRS
  Posted on WHO biological website for public comment

- April 2018, Beijing, China
  Informal consultation

- Jan.-Feb. 2018
  Comments provided by XMU and INNOVAX

- Jun. 2018
  The second draft of HEV TRS posted on WHO website

  Submit for final adoption in ECBS meeting
Cecolin® -- World's Brand-New HPV 16&18 Vaccine: VLP Produced in *E. coli* by a Member of DCVMN
HPV 16 & 18 Bivalent Vaccine Development

First HPV vaccine based on *E. coli* expression system

- 2002: Project initiated
- 2007: IND submitted in China
- Mar. 2010: Clinical trial approved
- Aug. 2011: Phase I finished
- Jan. 2012: Phase II finished
- Dec. 2012: Phase III initiated
- Dec. 2015: Bridging study for young girl, as well as for 2-dose regimen
- Nov. 2017: BLA submitted in China
- Sept. 2018: Clinical study inspection finished
- Nov. 2017: BLA submitted in China
- ~Jan. 2019: Launch in China
- ~May 2019: PQ submission
- 2020/2021?: PQ approval?
Target Product Profile of Cecolin®

- **Serotype**
  - 16 & 18 bivalent vaccine
  - 40µg HPV16 VLPs & 20µg HPV18 VLPs

- **Expression system**
  - *Escherichia coli* expressed L1-based vaccine

- **Target population**
  - women ages 9 - 45yr

- **Presentation**
  - 0.5 ml of suspension per dose in 2ml vial
  - 0.5ml of suspension per dose in pre-filled syringe
  - 1ml of suspension, 2 doses in 2ml vial (Gavi market)

- **Shelf-life**
  - 2 - 8°C 48 months in application, with 60 months data

- **Schedule**
  - 0, 1, 6 m (0, 6m for 9 -14 yrs)

- **With Alum adjuvant. No preservative.**
State of the Art Facility

Fermentation

Sterile Isolator
Wenzhou Weike, China

50-500L Fermentation System
Shanghai Sensong, China

Primary Purification

Centrifuge
GEA, Germany

Homogenizer
ATS, Germany

Ultra-filtration system
PALL, US

Ultra-filtration system
PALL, US

Chromatography
GE, US

Ultra-filtration system
PALL, US

Primary Purification

Ultra-filtration system
PALL, US

Vial Filling line
Marchesini, Italy

Syringe Filling line
Bosch, Germany

Aseptic Filling

Ultra-filtration system
PALL, US

Vial Filling line
Marchesini, Italy

Syringe Filling line
Bosch, Germany

Innovation For Life

2018-10-31

Confidential
Cecolin® - A New, Safe and Cost Effective HPV 16&18 Vaccine

The randomized controlled phase III clinical trial (7,372 participants) showed **Innovax HPV bivalent has compatible efficacy profile with published results by other manufacturers.**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Vaccine group</th>
<th>Control group</th>
<th>Efficacy% (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>No. of Case</td>
<td>N</td>
</tr>
<tr>
<td>HPV 16 and/or 18 related CIN2+/VIN2+/VaIN2+</td>
<td>INNOVAX bivalent vaccine</td>
<td>3306</td>
<td>0</td>
</tr>
<tr>
<td>Manufacturer 1</td>
<td>Bivalent vaccine</td>
<td>2524</td>
<td>1</td>
</tr>
<tr>
<td>Manufacturer 2</td>
<td>Quadirvalent vaccine</td>
<td>1265</td>
<td>0</td>
</tr>
<tr>
<td>HPV 16 and/or 18 related 6-month persistent infection</td>
<td>INNOVAX bivalent vaccine</td>
<td>3240</td>
<td>1</td>
</tr>
<tr>
<td>Manufacturer 1</td>
<td>Bivalent vaccine</td>
<td>2480</td>
<td>2</td>
</tr>
<tr>
<td>Manufacturer 2</td>
<td>Quadirvalent vaccine</td>
<td>1275</td>
<td>7</td>
</tr>
</tbody>
</table>

References:
2. Gardasil® package insert in China;
## Cecolin® - Non-inferiority of immunogenicity in Adolescent Girls with 2-dose Schedule

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Objective</th>
<th>Dosage</th>
<th>No. of participants</th>
<th>Conclusion/Status</th>
</tr>
</thead>
</table>
| Immunobridging   | Randomized, controlled  | • Safety and immunogenicity in female ages 9 to 17 in 3-dose schedule    | 60µg (HPV16:HPV18=2:1) at 0,6 month or 0,1,6 month                    | 975 women ages 9-26 yr | 1. Non-inferiority of immunogenicity has been demonstrated in 2-dose group (9-14y) and 3-dose younger age group (9-17y) compared with 3-dose adult group (18-26y).  
2. The candidate vaccine is well tolerated.                                             |
Cecolin® - AE in Clinical Studies (in China) with Compatible Results

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Most common ≥10%</th>
<th>Common 1-10%</th>
<th>Rare 0.1-1%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Local</td>
<td>Systemic</td>
<td>Local</td>
</tr>
<tr>
<td>INNOVAX bivalent vaccine</td>
<td>Pain, erythema, swelling</td>
<td>Fever, fatigue, Myalgia, headache</td>
<td>Hard knot, itching</td>
</tr>
<tr>
<td>Manufacturer 1</td>
<td>Pain, redness, swelling</td>
<td>Fever, fatigue, Myalgia, headache</td>
<td>Hard knot, itching</td>
</tr>
<tr>
<td>Manufacturer 2</td>
<td>Pain, redness, swelling</td>
<td>Fatigue, myalgia, headache, fever (≥37°C)</td>
<td>Joint pain, gastrointestinal symptoms (including nausea, vomit, diarrhea, and abdominal pain), urticaria and rashes</td>
</tr>
</tbody>
</table>

None of Serious Adverse Events (SAE) were related to vaccination
None adverse influence occured in pregnant women and newborns
Our HPV Vaccine Products for Global Market

Preclinical

Cecolin™ 9 HPV 9-valent vaccine
- Clinical trial approved on Nov. 2017
  ➢ Draft protocol of clinical study phase I & II has been completed;
  ➢ Phase I to be initiated in Feb.~Mar. 2019

Clinical Study

Cecolin® HPV 16/18 bivalent vaccine
- BLA submitted in Nov. 2017
- Clinical Inspection in Sept. 2018

IND

NDA

Approved
Two vaccines available for the global market

Develop HPV 9-valent vaccine
- Single-dose study for matching different market need

To develop more high quality innovative vaccines with cost-effective *E.coli* expression system
Thank you!

Xiamen Innovax Biotech Co., Ltd.