• Epidemic of EV71-associated HFMD
• Development of Sinovac’s EV71 Vaccine, *Inlive*
• Phase III Trial Design and Outcome
• Industrialization of EV71 Vaccine
• Summary
1975, in Bulgaria, 750 children cases, including 149 cases of acute flaccid paralysis and 44 deaths.

1998, Taiwan, 129,106 cases, including 405 critical cases and 78 deaths, 91% of deaths are children aged less than 5 years old.

1997, Malaysia, 2,628 cases, average age of 30 deaths is 1.5 years old.
EV71 Epidemic In China

In total 14 millions HFMD reported, with more than 3,350 fatal cases.

Serious HFMD epidemic in China;
EV71 inducing main serious and fatal cases;
Vaccine against EV71 is the answer.

《Hand, foot, and mouth disease in China, 2008–12: An epidemiological study》
Development Milestones

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>Preclinical Studies</td>
</tr>
<tr>
<td>2009</td>
<td>Applied for Clinical Trials</td>
</tr>
<tr>
<td>2010</td>
<td>Clinical Trials</td>
</tr>
<tr>
<td>2011</td>
<td>Commercial Plant Construction</td>
</tr>
<tr>
<td>2012</td>
<td>2010.12 Clinical Trial Application Approved</td>
</tr>
<tr>
<td>2013</td>
<td>2013.05 Applied for Production Approval</td>
</tr>
<tr>
<td>2014</td>
<td>2014.11 CFDA Experts Review</td>
</tr>
<tr>
<td>2015</td>
<td>2015.12.30 Approval</td>
</tr>
</tbody>
</table>

- Clinical Trials:
  - Phase I
  - Phase II
  - Phase III
  - 2011.05
  - 2011.11
  - 2013.03
Characters of Inlive™

- Vero Cell, cell factory cultivation technology;
- H07 strain, C4 genotype, isolated by China CDC;
- Inactivation with formaldehyde
- Al(OH)3 as adjuvant
- 100 u/200u/400 u, 2 doses/3 doses regimen
Pre-clinical Studies of Sinovac EV71 Vaccine

- Safety
  - Acute toxicity test
  - Local stimulation test
  - Allergy test
  - Repeated doses toxicity study (rat, cynomolgus monkey)

- Immunogenicity
  - Mice (immune dosage, ED50)
  - Rats (immunization schedule, longevity of serologic responses)

- Protection efficacy (neonatal mice)
  - Animal model was developed by the University of Sydney
  - Passive protection model
Establishment of Animal Model-Neonatal Mice

- Inoculation for the mother mice with antigen from 50u-800u at day 0 and 14 could cause 100% protection for the baby mice which were challenged MP-26M virus at 5 days after birth.
- Cross protection to different genotype has been approved in this animal model.
EV71 Vaccine Clinical Trails

**Phase I**
- **Objective:** Safety, Immunogenicity
- **Subjects:** Babies, children, and Adult
- **Dose:** 100U, 200U, 400U

**Phase II**
- **Objective:** Immunogenicity, safety
- **Subjects:** 6-35 months babies
- **Dose:** 100U, 200U, 400U

**Phase III**
- **Objective:** Protective effective
- **Subjects:** 6-35 months babies
- **Dose:** 400U

168 subjects

540 subjects

10077 subjects

1400 subjects

广西

江苏
## Phase III-Clinical Trial Design

**Multi-center, randomized, double-blinded, placebo-controlled**

**Immunization Schedule**: Day 0, 28  
**Dosage**: 400U/dose

<table>
<thead>
<tr>
<th><strong>Investigator</strong></th>
<th>Jiangsu CDC</th>
</tr>
</thead>
</table>
| **Lab Tests Technician** | **Virus isolation, PCR**: National Institutes for Viral Disease Control & Prevention, China CDC  
**Serum Tests**: National Institutes for Food and Drug Control (NIFDC) |
| **Statistician** | The Fourth Military Medical University |
| **Sponsor** | Sinovac Biotech Co., Ltd. |
| **Data and Safety Monitoring Board (DSMB)** | 5 members |
Phase III-Hypotheses & Sample Size Calculation

Hypothesis 1:
Vaccine Protection Rate would be 80%

Hypothesis 2:
Incidence in the placebo group would be 800/100,000

Sample Size:
10,000

Experimental Vaccine Group
5000

Placebo (Control) Group
5000

Surveillance Period: 1 Year

EV71 Incidence of 6-35 Months old Infants ranged 400-2000/100,000

National & Jiangsu Provincial HFMD Epidemic Surveillance Data

HFMD Epidemiological Data of 6 counties in Jiangsu (2010)
### Phase III-Subjects Grouping & Surveillance Design

#### Immunogenicity Subgroup

<table>
<thead>
<tr>
<th></th>
<th>Experimental</th>
<th>Control</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>6-11 Months</td>
<td>1250</td>
<td>1250</td>
<td>2500</td>
</tr>
<tr>
<td>12-23 Months</td>
<td>2500</td>
<td>2500</td>
<td>5000</td>
</tr>
<tr>
<td>24-35 Months</td>
<td>1250</td>
<td>1250</td>
<td>2500</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>5000</strong></td>
<td><strong>5000</strong></td>
<td><strong>10000</strong></td>
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</tbody>
</table>

**Total: 1200**

400 subjects from each of the 3 centers

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#### Primary Endpoint Efficacy

#### Secondary Endpoint Safety

#### Secondary Endpoint Immunogenicity Immune Persistency

#### Blood Sampling

- **Day0 28**
- **D0**
- **D56**
- **M8**
- **M14**
- **M26**

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#### Surveillance

<table>
<thead>
<tr>
<th>Year</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
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<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
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<td>4</td>
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<td>6</td>
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<td>9</td>
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<td>12</td>
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</table>

**Surveillance (1st Year)**

**Surveillance (2nd Year)**
**Phase III-Monitoring & Diagnosis of Cases**

**Case Detected**
- Reported by subjects’ parents
- Outpatients Information from Medical Institution

**Clinically Suspicious Cases**
- Collect Throat & Anal Swabs
- Fluorescence-based Quantitative PCR within 24 hrs

**Sampling & Tests**
- EV Negative Cases
- CA16 Positive Cases
- Other EV Positive Cases
- EV71 Positive Cases

- Follow-up Visit within 48 hrs
  - Collect throat & anal swabs, stool & blood samples for re-check

**Confirmed Cases**
- Clinical symptoms + PCR results → Preliminary diagnosis
- DSMB Review
  - Symptoms, duration, PCR results
  - (Virus isolation, neutralizing antibody test)

**Outpatients Information from Medical Institution**
Protection rate against EV71-associated disease (80%)
48 EV71-associated HFMD or Herpangina during 1 year of monitoring period

Safety
Day 0 – 56: incidences of solicited & unsolicited AE
Day 57 – Month 14: incidence of SAE

Immunogenicity (Immunogenicity subgroup)
In experimental group & control group at day 56: anti-EV71 neutralizing antibody positive rate, GMT, GMI

Immune persistency (Immunogenicity subgroup)
In experimental group & control group at M8 & M14: anti-EV71 neutralizing antibody positive rate, GMT, GMI

Explore the immunological surrogate of protection
Phase III-Subjects

12,446 volunteers been screened

2,369 were excluded

10,077 enrolled & randomly assigned into experimental or control group

Safety Analysis Set: 5,044 received 1st dose
5,044 received 1st dose
4,719 received 2nd dose

Safety Analysis Set: 5,033 received 1st dose
5,033 received 1st dose
4,711 received 2nd dose

Surveillance & primary efficacy analysis (intention-to-treat/full analysis set, FAS)

325 did not receive 2nd dose

322 did not receive 2nd dose

Experimental Group

132 discontinued the study

3 discontinued

Safety Analysis Set: 5,044
5,044 received 1st dose
4,719 received 2nd dose

Surveillance & primary efficacy analysis (intention-to-treat/full analysis set, FAS)

Efficacy analysis: per-protocol Set (PPS)
4,587

Control Group

322 did not receive 2nd dose

5 discontinued

Safety Analysis Set: 5,033
5,033 received 1st dose
4,711 received 2nd dose

Surveillance & primary efficacy analysis (intention-to-treat/full analysis set, FAS)

Efficacy analysis: per-protocol Set (PPS)
4,578

132 discontinued the study
Phase III-Surveillance Results (FAS)

Total 10077 subjects

EV71 Positive Case 119

PCR Virus isolation Neutralizing antibody DSMB Review & Confirmation

EV71-associated 99

EV71-associated herpangina cases 4

Other EV71 Positive Cases 20

EV71-associated HFMD 95

EV71-associated hospitalized HFMD 24

EV71-associated severe HFMD 8

Total 10077 subjects
### Phase III-Efficacy Results (FAS) 1st Year

Person-Year:
- Experimental: 4973.2
- Control: 4873.0

Incidence Density Rate (IDR) = (Case Number/Person-year) × 100%
Protection Rate = (Control Group IDR – Experimental IDR)/ Control Group IDR × 100%

<table>
<thead>
<tr>
<th>Case Classification</th>
<th>Case Number</th>
<th>Incidence Density (%, 95%CI)</th>
<th>Protection Rate (%, 95%CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EV71 Positive Cases</td>
<td>13</td>
<td>0.261</td>
<td>88.0 (78.6, 93.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EV71-associated diseases</td>
<td>5</td>
<td>0.101</td>
<td>94.8 (87.2, 97.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EV71-associated HFMD</td>
<td>5</td>
<td>0.101</td>
<td>94.6 (86.6, 97.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EV71-associated hospitalized HFMD</td>
<td>0</td>
<td>0.000</td>
<td>100.0 (83.7, 100.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EV71-associated severe HFMD</td>
<td>0</td>
<td>0.000</td>
<td>100.0 (42.6, 100.0)</td>
<td>0.0036</td>
</tr>
</tbody>
</table>

The Protection Efficacy of the vaccine reached the designed primary endpoint (80% for the 1st Year Surveillance)
**EV71 Vaccine - Efficacy**

- **Protection rate for EV71 infection**: 94.8%
- **Protection for hospitalized cases and serious cases**: 100.0%

---

**Effectiveness for EV71 Infection**

- Vaccine group: 5 cases
- Control: 94 cases

**Effectiveness for hospitalized cases**

- Vaccine group: 0 cases
- Control: 24 cases

**Protection rate for EV71 infection**: 94.8%

**Protection for hospitalized cases and serious cases**: 100.0%

---

56 days after vaccination, Neutralizing antibody positive rate 98.79%, GMT 165.79,
8 months and 14 months after vaccination, high level of antibody
Good immunogenicity and immune persistence.
Phase III-Safety Results

Incidence of each AE symptom ( % )

AE Incidence:
Experimental (5044): 51.7%
Control (5033): 52.8%
not statistically significant (p=0.2905)

Incidence of each Grade 3 AE symptom ( % )

No significant different between vaccine group and placebo group
Objective: to evaluate the lot-to-lot consistency, immunogenicity and safety of this EV71 vaccine candidate

Design: randomized, double-blinded, placebo-controlled

Sample size: 1400 (4 groups with 350 subject per group)

Immunization Schedule: Day0, 28

Immunogenicity indicator: neutralizing antibody level (Day 0, 56)

Safety indicator: systemic AE, local AE, SAE

<table>
<thead>
<tr>
<th></th>
<th>GMT Logarithmic difference (95% CI)</th>
<th>Criteria</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lot 1 vs. Lot 2</td>
<td>0.04 (-0.04 ~ 0.12)</td>
<td>-0.176 ~ 0.176</td>
<td>Equivalent</td>
</tr>
<tr>
<td>Lot 1 vs. Lot 3</td>
<td>0.02 (-0.06 ~ 0.10)</td>
<td></td>
<td>Equivalent</td>
</tr>
<tr>
<td>Lot 2 vs. Lot 3</td>
<td>-0.02 (-0.10 ~ 0.06)</td>
<td></td>
<td>Equivalent</td>
</tr>
</tbody>
</table>

Demonstrated Lot-to-lot Consistency
Industrialization

Production
19000 m²

4F
Ready for use

3F
QC Labs
EV71 Bulk
20 million does/year

2F
Formulation
Filling & Packaging
100 million doses/year

1F
Cold Room
1.8 million vials
Utilities

Others
4000 m²

2F
Animal Lab

1F
Biobank

Office
9000 m²

Total: 29,021 m²
Built-up area: 32,322 m²
EV71 Workshop

Capacity of 20 million doses per year

Large scale cells/virus cultivation
Completed an integral development process of EV71 vaccine
- Pre-clinical trial (protection animal model)
- Clinical trials (94.8% protection rate)

Built up vaccine production capacity of >20 million doses/year

Believe will play a significant role for HFMD control in China

Seek collaboration with other organization for HFMD control in other countries

Hope WHO could involve more in HFMD control
Suppyle vaccines to eliminate human diseases

谢谢！

中国儿童使用国际水平的疫苗
世界儿童使用中国生产的疫苗

Provide Chinese children with international quality vaccines
Provide children in the world with vaccines made in China