Use of Recombinant Zoster Vaccine (RZV) in Immunocompromised Populations

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Unmet Need: Patients With Immunocompromising Conditions Have a Higher Risk of HZ

Incidence Rates of HZ in Adult Patients

Bone marrow or stem cell transplant

Hematologic malignancies

Heart transplant

Renal transplant

Solid tumors

Liver transplant

HIV infection

Systemic lupus erythematosus

Rheumatoid arthritis

Inflammatory bowel disease

Multiple sclerosis

Psoriasis

Immunocompetent (all ages)

HIV, human immunodeficiency virus; HZ, herpes zoster.

Addressing the Unmet Need

• RZV demonstrated >90% efficacy in **Immunocompetent Older Adults (≥50 YOA)**\(^1\)\(^2\)
• No safety concerns identified in clinical trials\(^1\)\(^2\)
• RZV was licensed by FDA on October 20, 2017\(^3\)

**Addressing the Unmet Need in Immunocompromised (IC) Adults (≥18 YOA)**

IC populations are very heterogeneous, both across and within groups

• Not feasible to define every possible IC condition/medication combination

• Immune responses and vaccine safety in IC populations are primarily influenced by:
  – Age
  – Underlying disease
  – Immunosuppressive therapy (IS)
  – Timing of vaccination (before, during, after therapy)

IC, immunocompromised; IS, immunosuppressive; RZV, recombinant zoster vaccine; Vacc, vaccination; YOA, years of age
Addressing the Unmet Need

RZV Clinical Development Program in IC Populations

Phase I/II

- **Autologous Hematopoietic Stem Cell Transplant (auHSCT)**
  - Efficacy, Immunogenicity, Safety
  - N=1846

- **Human Immunodeficiency Virus (HIV)**
  - Immunogenicity, Safety
  - N=123

Phase III

- **Hematologic Malignancies (HM)**
  - Immunogenicity, Safety, Post-hoc Efficacy
  - N=562

- **Solid Tumors (ST)**
  - Immunogenicity, Safety
  - N=232

- **Renal Transplant (RT)**
  - Immunogenicity, Safety
  - N=264

*Phase II/III study.
IC, immunocompromised; RZV, recombinant zoster vaccine.

# Addressing the Unmet Need

## RZV Phase III Clinical Development in IC Populations

### Phase III

<table>
<thead>
<tr>
<th>Underlying Disease</th>
<th>Age</th>
<th>Immunosuppressive (IS) Treatment</th>
<th>Timing of Vaccination</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autologous Hematopoietic Stem Cell Transplant (auHSCT)</td>
<td>18+ (18-49, 50+)</td>
<td>Pre-HSCT conditioning, Post-HSCT therapy (+/- antivirals)</td>
<td>50-70d post-auHSCT</td>
<td>Efficacy, Immunogenicity, Safety</td>
</tr>
<tr>
<td>Hematologic Malignancies (HM)</td>
<td>18+ (18-49, 50+)</td>
<td>IS chemotherapy per SOC</td>
<td>During Chemo (+/- 10d) After Chemo (10d–6mo)</td>
<td>Immunogenicity, Safety, (Post-hoc Efficacy)</td>
</tr>
<tr>
<td>Solid Tumors (ST)</td>
<td>18+ (18-49, 50+)</td>
<td>IS chemotherapy per SOC</td>
<td>PreChemo† OnChemo†</td>
<td>Immunogenicity, Safety</td>
</tr>
<tr>
<td>Renal Transplant (RT)</td>
<td>18+ (18-49, 50+)</td>
<td>Chronic IS per SOC</td>
<td>&gt;4-18 mo post-allograft</td>
<td>Immunogenicity, Safety</td>
</tr>
</tbody>
</table>

*Phase II/III study. †Dose 1 given either 8-30 days before the start of a cycle (PreChemo group) or at the start of a cycle (OnChemo group).
Chemo, chemotherapy; d, day; IS, immunosuppressive; Mo, month; RZV, recombinant zoster vaccine; SOC, standard of care.
RZV Multicenter Studies in IC Populations Were Randomized, Observer-blinded, Placebo-controlled

IC population ≥18 YOA
Randomization 1:1 (RZV:Placebo)

- auHSCT
- HM
- RT
- ST

7d Solicited AEs
30d Unsolicited AEs
SAEs, pIMDs, Pregnanacies, HZ, Relapses, Disease Progression

RZV: / Placebo: 🔥
blood sampling for humoral immunogenicity; 🔧 blood sampling for cell-mediated immunity

AE, adverse event; auHSCT, autologous hematopoietic stem cell transplant; HM, hematologic malignancies, HZ, herpes zoster; IC, immunocompromised; M, month; pIMD, potential immune-mediated disease; RT, renal transplant; RZV, recombinant zoster vaccine; SAE, serious adverse event; ST, solid tumor; YOA, years of age.

Pooled Reactogenicity in Immunocompromised Patients

Solicited local AEs were mostly mild/moderate in intensity and lasted a median of 3 days. Grade 3 solicited local AEs had a median duration of 1-2 days.
Any Systemic | Fatigue | Myalgia | Headache | Gastrointestinal symptoms | Shivering | Fever (≥37.5°C )
---|---|---|---|---|---|---
RZV 18–49 YOA (n=436) | 82.1 | 73.7 | 60.8 | 48.9 | 27.3 | 25.2 | 19.2
RZV ≥50 YOA (n=1117) | 64.7 | 55.6 | 50.4 | 32.2 | 27.3 | 14.4 | 9.8
Placebo 18–49 YOA (n=407) | 55.8 | 42 | 38.5 | 23.7 | 27.3 | 11.5 | 6.6
Placebo ≥50 YOA (n=1081) | 50.6 | 38.5 | 23.7 | 14.4 | 11.5 | 6.6 | 3.8

% of participants reporting systemic AEs

**Solicited general AEs were mostly mild/moderate and lasted ≤3 days. Grade 3 solicited general AEs lasted ≤2 days (median duration)**

Graph reproduced from Fauqued ML, 2020. Presented at IDWeek 2020

Grade 3 was defined as follows: pain that prevented normal activity; >100 mm diameter for redness and swelling; symptoms that prevented normal activity for headache, myalgia, fatigue and gastrointestinal symptoms; fever >39.0°C (axillary/oral temperature).

For the systemic AEs fatigue, headache (all, related), myalgia, shivering, and fever (all, related) were reported with higher incidences in the RZV 18–49 YOA group than in the RZV ≥50 YOA group. AE, adverse event; RZV, recombinant zoster vaccine; TVC, total vaccinated cohort; YOA, years of age.

Unsolicited Adverse Events (AEs)
Percentage of participants reporting ≥1 unsolicited AE 30 days post-vaccination per study – TVC

Error bars represent 95% CI. Each population was evaluated in a separate study. There are no head-to-head comparisons between immunocompromised populations. AE, adverse event; auHSCT, autologous hematopoietic stem cell transplant; CI, confidence interval; HM, hematological malignancies; RT, renal transplant; RZV, recombinant zoster vaccine; ST, solid tumors patients; TVC, total vaccinated cohort; YOA, years of age.


Across studies, the percentage of adults reporting ≥1 unsolicited AE was similar between RZV and placebo groups.
Serious Adverse Events (SAEs)

Percentage of participants reporting ≥1 SAE from dose 1 until 1-year post-last dose per study – TVC

Error bars represent 95% CI. Each population was evaluated in a separate study. There are no head-to-head comparisons between immunocompromised populations. The percentage of adults with ≥1 SAE, causally related SAEs, fatal SAEs and pIMDs was similar between RZV and placebo and between age groups.

auHSCT, autologous hematopoietic stem cell transplant; CI, confidence interval; HM, hematological malignancies; RT, renal transplant; RZV, recombinant zoster vaccine; SAE, serious adverse event; ST, solid tumors patients; TVC, total vaccinated cohort; YOA, years of age.

Potential immune mediated diseases (pIMDs)

Percentage of participants reporting ≥1 pIMD during selected study periods – TVC (pooled)

Data on file, 2021N477632.
Safety: Underlying Disease-related Events

- Proportion of patients with disease progressions or disease relapse were balanced between RZV and placebo groups.
- 4 biopsy-confirmed allograft rejections in the RZV group.
- 7 biopsy-confirmed allograft rejections in the placebo group.
- No impact on renal-allograft function based on serum creatinine levels.

Each population was evaluated in a separate study. **There are no head-to-head comparisons between immunocompromised populations.**

auHSCT, autologous hematopoietic stem cell transplant; HM, hematologic malignancies, RT, renal transplant; RZV, recombinant zoster vaccine.

Vaccine Efficacy in Immunocompromised Patients

Pivotal Vaccine Efficacy: auHSCT
Post-hoc Vaccine Efficacy: HM

auHSCT, autologous hematopoietic stem cell transplant; HM, hematologic malignancies
# Vaccine Efficacy in IC Patients

## First or only episode of HZ – mTVC

<table>
<thead>
<tr>
<th></th>
<th>RZV</th>
<th>Placebo</th>
<th>VE (95% CI)</th>
<th>Median follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>n</td>
<td>HZ Incidence Rate (per 1000 person-years)</td>
<td>N</td>
</tr>
<tr>
<td>auHSCT(^1,2)</td>
<td>870</td>
<td>49</td>
<td>30</td>
<td>851</td>
</tr>
<tr>
<td>18-49</td>
<td>213</td>
<td>9</td>
<td>21.5</td>
<td>212</td>
</tr>
<tr>
<td>≥50</td>
<td>657</td>
<td>40</td>
<td>33</td>
<td>639</td>
</tr>
<tr>
<td>PHN</td>
<td>870</td>
<td>1</td>
<td>0.5</td>
<td>851</td>
</tr>
<tr>
<td>HM(^3)*</td>
<td>259</td>
<td>2</td>
<td>8.5</td>
<td>256</td>
</tr>
</tbody>
</table>

\(^1\)Efficacy was evaluated in a post-hoc analysis.  
\(^2\)There are no head-to-head comparisons between immunocompromised populations.  
\(^3\)auHSCT, autologous hematopoietic stem cell transplant; CI, confidence interval; HM, hematologic malignancies; HZ, herpes zoster; IC, immunocompromised; mTVC, modified total vaccinated cohort; N, number of subjects included in each group; n, number of subjects having at least one confirmed HZ episode; VE, vaccine efficacy (Poisson method).

Vaccine Immunogenicity

RZV Multicenter Studies in IC Populations Were Randomized, Observer-blinded, Placebo-controlled

IC population ≥18 YOA
Randomization 1:1 (RZV:Placebo)

AE, adverse event; auHSCT, autologous hematopoietic stem cell transplant; HM, hematologic malignancies, HZ, herpes zoster; IC, immunocompromised; M, month; plMD, potential immune-mediated disease; RT, renal transplant; RZV, recombinant zoster vaccine; SAE, serious adverse event; ST, solid tumor; YOA, years of age.

RZV Humoral Mediated Immunity

Anti-gE GMCs (ELISA) Pre-, 1 month post dose 2, and 12 months post last dose – ATP cohort for immunogenicity

Error bars represent 95% CI. Each population was evaluated in a separate study. There are no head-to-head comparisons between immunocompromised populations.

auHSCT, autologous hematopoietic stem cell transplant; ATP, according to protocol; gE, glycoprotein E; GMC, geometric mean concentration; HM, hematologic malignancies; RT, renal transplant; RZV, recombinant zoster vaccine; ST, solid tumor; ZOE-50, Zoster Older adults Efficacy trial in ≥50 years of age.

RZV Cellular Mediated Immunity

Median Frequency for gE-specific CD4+ T-cells Pre-, 1 Month post dose 2, and 12 Months post last dose – ATP cohort for immunogenicity

Error bars represent 1st and 3rd IQR. Each population was evaluated in a separate study. **There are no head-to-head comparisons between immunocompromised populations.**

*For ST study: on-chemo group (1st dose administered 8-30 days before chemotherapy and 2nd dose on the day of chemotherapy).

auHSCT, autologous hematopoietic stem cell transplant; ATP, according to protocol; gE, glycoprotein E; IQR, interquartile range; HM, hematologic malignancies; RT, renal transplant; RZV, recombinant zoster vaccine; ST, solid tumor; ZOE-50, Zoster Older adults Efficacy trial in ≥50 years of age.

Addressing the Unmet Need

RZV Clinical Development Program in IC Patients

- Reactogenicity profile is expected based on clinical experience and nature of underlying conditions
- AEs, SAEs, pIMDs, relapses, disease progressions, and allograft rejections were balanced between the RZV and placebo groups
- Efficacy demonstrated in 2 populations: 68.2% (95% CI: 55.6-77.5) in auHSCT recipients and 87.2% (95% CI: 44.3-98.6) in HM* patients
- RZV is immunogenic even considering the impact of age, underlying disease, immunosuppressive treatment and immunization either before, during or after immunosuppressive treatments

RZV immunogenicity and safety data support a favorable benefit-risk profile in IC adults ≥18 YOA, who are at an increased risk of HZ

*Efficacy was evaluated in a post-hoc analysis. Each population was evaluated in a separate study. There are no head-to-head comparisons between immunocompromised populations.

AE, adverse event; auHSCT, autologous hematopoietic stem cell transplant; HM, hematologic malignancies; HZ, herpes zoster; IC, immunocompromised; pIMD, potential immune-mediated disease; RT, renal transplant; RZV, recombinant zoster vaccine; SAE, serious adverse event; ST, solid tumor; YOA, years of age.

Addressing the Unmet Need in IC Adults (≥18 YOA)¹⁻⁶

- IC populations are very heterogeneous, both across and within groups
- Not feasible to define every possible IC condition/medication combination

### Addressing the Unmet Need

- **Phase II/III study**

### Additional populations

- Immune-compromising conditions
- Comorbid conditions
- Autoimmune conditions
- Immunosuppressive therapies

### Underlying Disease

- HIV
- auHSCT
- ST*
- RT
- HM

### Timing of Vacc.

- Age
- IS therapy

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¹Phase II/III study
IC, immunocompromised; IS, immunosuppressive; RZV, recombinant zoster vaccine; Vacc, vaccination; YOA, years of age.

Thank You