Randomized Phase 2 Trial of Felzartamab in Humoral Transplant Rejection

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Antibody-Mediated Kidney Transplant Rejection

- Late antibody-mediated kidney transplant rejection (AMR) is the leading cause of transplant loss\(^1\)

- Long-term outcomes after AMR diagnosis remain poor\(^2\)

- No therapeutic strategies have demonstrated efficacy
  - IL-6 blockade: Clazakizumab\(^3,4\)
  - B cell depletion: Rituximab\(^5\)
  - Complement inhibition: Eculizumab\(^6\)
  - Proteasome inhibition: Bortezomib\(^7\)

- There exists an unmet need for treatment of AMR

### Late active AMR & Allograft survival\(^2\)

- Death-censored graft survival
  - 12 months, 88.9%
  - 36 months, 58.9%
  - 60 months: 30.7%

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\(^1\)Mayrdorfer et al., J Am Soc Nephrol. 2021
\(^2\)Irish et al., Transplantation. 2021
\(^3\)Doberer et al., J Am Soc Nephrol. 2021
\(^4\)Phase 3: IMAGINE Trial (NCT03744910)
\(^5\)Moreso et al., Am J Transplant. 2018
\(^6\)Kulkarni S et al., Am J Transplant. 2017
\(^7\)Eskandary et al., J Am Soc Nephrol. 2018
CD38 Antibody Felzartamab in Late AMR

CD38
- Multifunctional receptor and enzyme
- Expressed on various types of immune cells:
  ✓ highest expression on plasma cells
  ✓ expression on subsets of: NK cells, T cells, B cells, and myeloid cells

Felzartamab
- Human IgG1λ CD38 antibody
- Primary mode of action:
  ✓ Lysis of target cells via antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis
  ✓ but not complement-dependent cytotoxicity

1 Boxhammer et al. Blood 2015; 126: 3015 (abstract)
Trial Scheme and Study Flow

**Key inclusion criteria**
- DSA+ active or chronic active AMR
- eGFR >20 mL/min/1.73m²
- ≥180 days post-transplant

**Primary outcome**
- Safety and tolerability

**Key secondary outcomes**
- AMR activity
- DSA characteristics
- NK and plasma cell counts
- dd-cfDNA
- eGFR slope

**Screening**
N=31

**N=22**
1:1 randomized

**Sites:**
Vienna
Berlin

**Randomized, double-blind, placebo-controlled, parallel-group phase 2 pilot trial**

**Felzartamab (n=11)**

**Placebo (n=11)**

**Observational Period**

Weeks
0 4 8 12 16 20 24 28 32 36 40 44 48 52

**Baseline biopsy**

**24-Week biopsy**

**52-Week biopsy**

One graft loss

22 were included in the intention-to-treat analysis

AMR, Antibody-mediated rejection; DSA, Donor-specific antibody; dd-cfDNA, Donor-derived cell-free DNA; eGFR, estimated glomerular filtration rate
Key Patient Characteristics at Baseline

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=11)</th>
<th>Felzartamab (N=11)</th>
<th>Total (N=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex – no. (%)</td>
<td>7 (63.6)</td>
<td>4 (36.4)</td>
<td>11 (50.0)</td>
</tr>
<tr>
<td>Median recipient age (IQR) – yr</td>
<td>56 (49–64)</td>
<td>42 (35–50)</td>
<td>50 (39–59)</td>
</tr>
<tr>
<td>Preformed anti-HLA DSA – no. (%)†</td>
<td>4 (36.4)</td>
<td>4 (36.4)</td>
<td>8 (36.4)</td>
</tr>
<tr>
<td>Median time after Tx (IQR) – yr</td>
<td>10 (6–19)</td>
<td>9 (6–14)</td>
<td>9 (5–18)</td>
</tr>
<tr>
<td>Median eGFR (IQR) – mL/min/1.73 m²</td>
<td>36 (31–43)</td>
<td>60 (35–69)</td>
<td>37 (33–64)</td>
</tr>
<tr>
<td>Median protein/crea ratio (IQR) – mg/g</td>
<td>1338 (187–1614)</td>
<td>690 (232–1248)</td>
<td>993 (178–1510)</td>
</tr>
<tr>
<td>Triple immunosuppression – no. (%)</td>
<td>9 (81.8)</td>
<td>9 (81.8)</td>
<td>18 (81.8)</td>
</tr>
<tr>
<td>Tacrolimus-based – no. (%)</td>
<td>8 (72.7)</td>
<td>10 (90.9)</td>
<td>18 (81.8)</td>
</tr>
<tr>
<td>Banff 2019 AMR phenotypes – no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active AMR</td>
<td>3 (27.3)</td>
<td>4 (36.4)</td>
<td>7 (31.8)</td>
</tr>
<tr>
<td>Chronic active AMR</td>
<td>8 (72.7)</td>
<td>7 (63.6)</td>
<td>15 (68.2)</td>
</tr>
<tr>
<td>DSA characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-DQ DSA – no. (%)</td>
<td>5 (45.5)</td>
<td>6 (54.5)</td>
<td>11 (50.0)</td>
</tr>
<tr>
<td>Peak MFI of DSA &gt;10,000 – no. (%)</td>
<td>3 (27.3)</td>
<td>5 (45.5)</td>
<td>8 (36.4)</td>
</tr>
</tbody>
</table>

† Pre-transplant DSA data were available for 14 recipients
## Primary Outcome: Safety of Felzartamab

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=11)</th>
<th>Felzartamab (N=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with AE – no. (%)</td>
<td>11 (100)</td>
<td>11 (100)</td>
</tr>
<tr>
<td>Number of AE</td>
<td>81</td>
<td>119</td>
</tr>
<tr>
<td>Patients with a TEAE – no. (%)</td>
<td>9 (81.8)</td>
<td>11 (100)</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>61</td>
</tr>
<tr>
<td>Mild</td>
<td>11 (100)</td>
<td>11 (100)</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>55</td>
</tr>
<tr>
<td>Moderate</td>
<td>1 (9.1)</td>
<td>2 (18.2)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Severe</td>
<td>1 (9.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Patients with a TRAE – no. (%)</td>
<td>7 (63.6)</td>
<td>10 (90.9)</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>27</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>0 (0)</td>
<td>8 (72.7)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>8</td>
</tr>
</tbody>
</table>

Eight infusion-related reactions: mild to moderate severity
- Limited to first dose
- Symptomatic treatment and reduced infusion rate
- No treatment discontinuations

AE, Adverse event; RSV, Respiratory syncytial virus; SAE, Serious adverse event; TEAE, Treatment-emergent adverse event; TRAE, Treatment-related adverse event
**Reduction in AMR Activity**

Resolution of AMR activity at Week 24:
- **Felzartamab:** 9/11 patients (81.8%)
- **Placebo:** 2/10 patients (20.0%)

**Difference:** 61.8%
(95% CI: 18.6%, 100%)
**Relative Risk (RR):** 0.23
(95% CI: 0.06, 0.83)

Recurrence of AMR activity at Week 52:
- 3/9 of Felzartamab-treated patients (33%)

*One patient in the placebo group lost their graft prior to Week 24 due to ongoing chronic active AMR.
Reduction in Microvascular Inflammation

MVI score at Week 24: median (IQR)

Felzartamab: 0 (0–1)
Placebo: 2.5 (2–3)

Mean difference between groups: −1.95 (95% CI: −2.97, −0.92)

MVI score of 0 at Week 24:

Felzartamab: 7/11 (63.6%)
Placebo: 1/10 (10%)
Reduction in Molecular AMR and Injury

MMDx® Molecular AMR classifier (AMR_{Prob})

- **AMR_{Prob}**
  - Baseline
  - Week 24
  - Week 52

- **Placebo**
- **Felzartamab**

No molecular features of TCMR

Injury biomarker

- **dd-cfDNA (%)**
- Placebo
- Felzartamab

MMDx, The Molecular Microscope® Diagnostic System; TCMR, T cell-mediated rejection
dd-cfDNA, Donor-derived cell-free DNA
Reduction in NK Cell Count and Burden

**Peripheral NK Cell Counts**

- NK Cell Counts
- Placebo
- Felzartamab
- Weeks: 0, 24, 52
- Cells, n/μL

**MMDx® Molecular NK Cell Burden (NKB)**

- NKB
- Score
- Baseline, Week 24, Week 52
- Placebo
- Felzartamab

MMDx, The Molecular Microscope® Diagnostic System
Levels of Donor-specific Antibodies (DSA)

**Immunodominant DSA levels**

- **DSA MFI**
  - Placebo
  - Felzartamab

**Immunoglobulin G level**

- **IgG**
  - Placebo
  - Felzartamab

Graphs showing changes in DSA MFI and IgG levels over time with Placebo and Felzartamab groups.
Overall Immunosuppressive Burden

No overall increases in infection-related AEs/SAEs

Torque Teno Virus (TTV) Load

TTV is a non-pathogenic commensal virus and a marker of functional immunity
Kidney Function and Proteinuria

**eGFR slope**

**Predicted eGFR**

- **Felzartamab**: $-0.39 \text{ mL/min/1.73 m}^2 \text{ per year}$
  
  (95% CI: $-5.47, 4.69$)

- **Placebo**: $-4.53 \text{ mL/min/1.73 m}^2 \text{ per year}$
  
  (95% CI: $-9.83, 0.77$)

**Urinary Protein-Creatinine Ratio**

No difference between groups

eGFR, estimated glomerular filtration rate; CI, Confidence interval
Summary

Safety
Felzartamab has an overall acceptable safety profile
No increase in SAEs
No signs of increased infection risk/over-immunosuppression
No treatment discontinuation due to AEs
No clinical/molecular evidence of TCMR

Mild to moderate 1st dose infusion-related reactions: 8/11 patients (73%)

Efficacy
Considerable effect size: Resolution of AMR activity in 9/11 patients (82%)
Recurrence of AMR activity: 6 months after end of treatment

Felzartamab has the potential as a new therapeutic option for AMR warranting further investigation

AE, Adverse events; AMR, Antibody-mediated rejection; SAE, Serious AE; TCMR, T cell-mediated rejection
The trial was funded by an unrestricted grant from MorphoSys AG and, after transfer of exclusive rights to develop felzartamab, Human Immunology Biosciences, Inc. (to Georg A. Böhmig)
A Randomized Phase 2 Trial of Felzartamab in Antibody-Mediated Rejection