Sprifermin Case Study

Marc C. Hochberg, MD, MPH
Professor of Medicine and Epidemiology and Public Health Head, Division of Rheumatology and Clinical Immunology Vice Chair, Department of Medicine
Sprifermin

- Sprifermin is a novel recombinant human fibroblast growth factor-18 (rhFGF-18) that is being developed as a potential disease-modifying OA drug (DMOAD).
- Sprifermin induces hyaline cartilage formation in vitro by increasing chondrocyte proliferation, resulting in increased overall extracellular matrix production.\(^1\)
- A 1-year, placebo-controlled, Proof of Concept (PoC) phase Ib study reported statistically significant, dose-dependent effects on total and lateral cartilage thickness in patients treated with intra-articular sprifermin.\(^2\)
- A 5-year, placebo-controlled phase II study (FORWARD) reported statistically significant, dose-dependent effects on total cartilage thickness in patients treated with intra-articular sprifermin after 2 years.\(^3\)

---

FORWARD Trial

- 5-year randomized placebo-controlled phase II dose-finding study of IA sprifermin in persons aged 40-85 with symptomatic knee OA
  - KL grade 2 or 3, medial mJSW >= 2.5 mm
  - Score of 4-9 on WOMAC A1
- Pre-specified primary analysis at 2 years
- Primary endpoint: Change in total femorotibial joint cartilage thickness in the index knee from baseline to 2 years measured by qMRI.
  - Change in WOMAC total and subscale scores was a secondary endpoint

**Study Design**

**Treatment Period** (2 years)
- Group 1: Sprifermin 100 µg q6 mo
- Group 2: Sprifermin 100 µg q12 mo
- Group 3: Sprifermin 30 µg q6 mo
- Group 4: Sprifermin 30 µg q12 mo
- Placebo

**Extended follow-up** (3 years)

**Screening**
- Symptomatic knee osteoarthritis
- KLG 2-3

**Major efficacy assessments:**

- q6mo, every 6 months active cycles; q12 mo, every 12 months active cycles
Primary Endpoint: Total TFJ Cartilage Thickness
Mean Change from Baseline Over 2 Years (mITT)

At baseline, total cartilage thickness was similar in all treatment arms and averaged ~1.8 mm.

TFJ, total femorotibial joint.

Treatment effect $p<0.001$
Dose response $p<0.001$
Secondary Imaging Endpoints

• Results consistent for both Medial and Lateral TFJ cartilage thickness as well as both the central medial and central lateral TFJ subregions
• Significant dose-response and treatment effect for lateral but not medial mJSW.
Secondary Endpoint: Total WOMAC Score
Mean (95% CI) Change from Baseline Over 2 Years (ITT)

All treatment groups had a mean decrease of ~50% in total WOMAC score (baseline total WOMAC score ~40)
No significant differences between treatment groups for WOMAC Pain, Physical Function and Stiffness subscale scores.
Main 3-year Exploratory Endpoint: TFTJ Cartilage Thickness
Mean Change from Baseline Over 2 Years (mITT)

- **Treatment effect P<0.001**
- **Dose response P<0.001**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose</th>
<th>Cycle</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td>82</td>
</tr>
<tr>
<td>30 µg q12 mo</td>
<td>n=93</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 µg q6 mo</td>
<td>n=85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 µg q12 mo</td>
<td>n=93</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 µg q6 mo</td>
<td>n=89</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Change from baseline in total cartilage thickness (mm)**
- **Last treatment cycle**
- **3 weekly injections**

- Δ=0.05mm

*P values represent baseline to 36 months
Difference from placebo in mean [95% CI] and P-value† absolute change from baseline:
- 0.05 mm [0.03–0.07] 100 µg q6mo; P=0.001
- 0.02 mm [-0.01–0.04] 100 µg q12mo; P=0.193
- 0.01 mm [-0.01–0.03] 30 µg q6mo; P=0.330
- -0.02 mm [-0.04–0.01] 30 µg q12mo; P=0.160

†The 95% CI and t-test P value are calculated by considering unequal variance
The significant 0.05 mm mean increase in TFTJ cartilage thickness with sprifermin 100 µg q6mo vs placebo at Year 2 was sustained to Year 5 — 0.05 mm (95% CI: 0.00, 0.10)

CI, confidence interval; mITT, modified intent-to-treat; TFTJ, total femorotibial joint; q6mo, every 6 months; q12mo, every 12 months
Change in TFTJ cartilage thickness up to year 5 in the (A) mITT population (n=494) and (B) SAR (n=161)
5-YEAR CHANGE IN WOMAC PAIN SCORE

Mean (95% CI) Absolute Change from Baseline at Year 2 and in the Follow-up Period

- The 50% improvement in WOMAC pain at Year 2 was maintained to Year 5 in all cohorts in the ITT population
- No significant treatment effect comparing any dose of sprifermin with placebo

**ITT POPULATION (n=549)**

Dose response at Year 5, $P = 0.673$

*Δ adjusted mean difference to placebo (scale 0-100)
CI, confidence interval; ITT, intent-to-treat; q6mo, every 6 months; q12mo, every 12 months; WOMAC, Western Ontario and McMaster Universities osteoarthritis index
Change from baseline in WOMAC pain scores up to year 5 in the (A) ITT population (n=549) and (B) SAR (n=161)

\[ \Delta_{\text{adj.}} = -1.1 \]
\[ (95\% \text{ CI} -9.1, 6.7) \]
SAFETY UP TO YEAR 5

- There were no clear differences in the nature, severity or type of reported AEs or SAEs between sprifermin groups and placebo
- A total of 15 patients had knee replacements, none of whom were in the sprifermin 100 µg q6mo group

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>ITT POPULATION</th>
<th>SUBGROUP AT RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo n=108</td>
<td>30 µg q12mo n=110</td>
</tr>
<tr>
<td>All AEs</td>
<td>105 (98.1)</td>
<td>107 (98.2)</td>
</tr>
<tr>
<td>Local AEs</td>
<td>52 (48.6)</td>
<td>54 (49.5)</td>
</tr>
<tr>
<td>Systemic AEs</td>
<td>103 (96.3)</td>
<td>104 (95.4)</td>
</tr>
<tr>
<td>All SAEs</td>
<td>39 (36.4)</td>
<td>35 (32.1)</td>
</tr>
<tr>
<td>Local SAEs</td>
<td>5 (4.7)</td>
<td>4 (3.7)</td>
</tr>
<tr>
<td>SAEs leading to death</td>
<td>1 (0.9)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Knee replacements</td>
<td>4 (4.6)</td>
<td>4 (4.0)</td>
</tr>
</tbody>
</table>

AEs, adverse events; ITT, intent-to-treat; SAEs, serious adverse events; q6mo, every 6 months; q12mo, every 12 months
FORWARD Trial: Conclusions

- The longest phase II DMOAD trial reported
- Sprifermin at a dose of 100 ug administered IA weekly for 3 doses every 6 months significantly increased TFJ cartilage thickness but did not significantly reduce symptoms as measured by WOMAC
- Post-hoc analysis of a “subgroup at risk” suggested translation of the structural benefit to clinical benefit
- Thus, a target dose and patient population have been identified for future phase III studies.
Thank you for your attention.