Fitusiran, an Investigational RNAi Therapeutic Targeting Antithrombin for the Treatment of Hemophilia: Interim Results from a Phase 2 Extension Study in Patients with Hemophilia A or B with and Without Inhibitors

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Fitusiran is an investigational medicine. Its safety and efficacy have not been established by any health authorities.
Fitusiran
Investigational RNAi Therapeutic for Treatment of Hemophilia

**Fitusiran (ALN-AT3)**
- SC-administered small interfering RNA (siRNA) therapeutic targeting antithrombin (AT)
  - Non-biologic, chemically-synthesized, with targeting ligand to specifically deliver to liver—site of AT synthesis
  - Harnesses natural RNA interference (RNAi) mechanism for regulation of plasma AT levels

**Therapeutic hypothesis**
- Hemophilia A and B are bleeding disorders characterized by ineffective clot formation due to insufficient thrombin generation
- Fitusiran is designed to lower AT, with goal of promoting sufficient thrombin generation to restore hemostasis and prevent bleeding
  - Observation of ameliorated bleeding phenotype in patients with co-inheritance of thrombophilic traits in hemophilia
  - Supported by pre-clinical data and emerging Phase 1 clinical results

The clinical significance of fitusiran’s mechanism of action is under investigation.

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Fitusiran Phase 2 Open-Label Extension (OLE) Study Design & Patient Disposition

Patients previously dosed in Phase 1* study eligible to roll over onto Phase 2 OLE^ study

Phase 1, Part B (N=12 patients with HA or HB)

- 15, 45, 75 mcg/kg weekly x 3 SC

Phase 1, Part C (N=18 patients with HA or HB)†

- 225, 450, 900, 1800 mcg/kg, or 80 mg monthly x 3 SC

Phase 1, Part D (N=16 patients with HA or HB; with inhibitors)

- 50, 80 mg monthly x 3 SC

Phase 2 OLE‡ (n=33)

- 50 mg monthly SC
- 80 mg monthly SC

- Individual patient dose adjustment may be allowed (per SRC)
- Days between doses in Phase 1 and Phase 2 OLE ranged from 30 (no interruption in dosing) to 461

HA, hemophilia A; HB, hemophilia B; SC, subcutaneous


†ClinicalTrials.gov Identifier: NCT02554773; EudraCT: 2015-001395-21

‡5 patients participating in Part C previously participated in Part B

‡3 patients started Phase 2 OLE at their original Phase 1 dose; later they were converted to 50 mg or 80 mg

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## Interim Fitusiran Phase 2 Open-Label Extension (OLE) Study Results*

### Patient Demographics & Exposure

*Data transfer 15June2017
†Doses denote current dose

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### Patients without Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>50 mg† N=10</th>
<th>80 mg† N=9</th>
<th>50 mg† N=3</th>
<th>80 mg† N=11</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years; mean (range)</strong></td>
<td>36 (19 – 61)</td>
<td>40 (24 – 58)</td>
<td>31 (22 – 36)</td>
<td>34 (21 – 41)</td>
</tr>
<tr>
<td><strong>Weight, kg; mean (range)</strong></td>
<td>78 (58 – 94)</td>
<td>73 (58 – 80)</td>
<td>82 (70 – 100)</td>
<td>72 (52 – 108)</td>
</tr>
<tr>
<td>Hemophilia A</td>
<td>7</td>
<td>7</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Hemophilia B</td>
<td>3</td>
<td>2</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Severe</td>
<td>9</td>
<td>7</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Moderate</td>
<td>1</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Positive Medical history for hepatitis C</td>
<td>8</td>
<td>8</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Exposure, months; median (range)</td>
<td>13 (5 – 20)</td>
<td>14 (3 – 18)</td>
<td>11 (5 – 12)</td>
<td>6 (0 – 12)</td>
</tr>
</tbody>
</table>

**Maximum of 20 months (median 11 months) of fitusiran dosing in Phase 2 OLE**

- Total of 359 months of patient exposure to fitusiran
Interim Fitusiran Phase 2 Open-Label Extension (OLE) Study Results*
Patient Disposition

33 Patients Enrolled

5 Patients Discontinued Dosing
• 4 due to withdrawal of consent†
• 1 due to AE‡

28 Patients Continued Dosing

*Data transfer 15 June 2017
AE, adverse event
† Withdrawal of consent due to: incarceration (1), to receive DAA therapy for HCV (1), following seizure (1), following hypertension (1)
‡ Discontinuation due to AE: asymptomatic AST and ALT elevation in patient with chronic HCV infection

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Interim Fitusiran Phase 2 Open-Label Extension (OLE) Study Results*

Safety/Tolerability

• 6 patients reported SAEs†
  ◦ 2 with SAEs considered possibly related to study drug
    – Asymptomatic ALT and AST elevation in patient with chronic HCV infection; led to discontinuation
    – Seizure with confusion in patient with history of seizure disorder

• 70% of patients reported an AE
  ◦ Majority of AEs were mild or moderate in severity and unrelated to study drug
  ◦ Non-laboratory AEs reported in >2 patients: injection site reactions (ISRs) 6/33 (18%), abdominal pain 3/33 (9%), diarrhea 3/33 (9%), headache 3/33 (9%)
    – ISRs all mild and transient

• ALT increases >3x ULN observed in 11 patients (all confirmed HCV antibody positive)
  ◦ All asymptomatic; no elevations of bilirubin >2x ULN
  ◦ All cases are resolved (10) or resolving (1)
    – 8 without dose interruption

• No thromboembolic events
  ◦ No clinical or laboratory evidence of pathologic clot formation
  ◦ All bleed events successfully managed with replacement factor or bypassing agent

• No instances of drug-induced anti-drug antibody formation

*Data transfer 15June2017
†4 Patients with unrelated SAEs: acute gastroenteritis and cholecystitis (1), gastroesophageal reflux disease, asthma and infective exacerbation of asthma (1), COPD (1), Duodenal ulcers (1)

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Context for Transaminase Elevations

Fitusiran is a liver-directed therapy and low frequency of ALT changes with other molecules in our platform have been reported

However, chronic HCV infection has been associated with elevated ALT and thus represents an important confounder

Transaminase elevations have been observed in populations with chronic HCV infection

- In a study of 280 asymptomatic blood donors with chronic HCV infection†
  - 17% had normal ALT levels
  - 45% had ALT elevations >1-2x ULN
  - 16% had ALT elevations >2-5x ULN
  - 22% had ALT elevations >5x ULN
- In a 2015 report of ledipasvir-sofosbuvir treatment for chronic HCV infection‡, LFT monitoring of 77 patients treated with placebo over 12 weeks showed
  - 74% with normal ALT levels
  - 3% with ALT elevations >1-3x ULN
  - 14% with ALT elevations >3-5x ULN
  - 9% with ALT elevations >5x ULN

Phase 3 studies will exclude patients with chronic HCV infection; such patients may be enrolled after curative treatment


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Interim Fitusiran Phase 2 Open-Label Extension (OLE) Study Results*

Antithrombin Levels and Thrombin Generation

**Antithrombin Levels**

<table>
<thead>
<tr>
<th>Days since first dose</th>
<th>1</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>180</th>
<th>270</th>
<th>360</th>
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</thead>
<tbody>
<tr>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>N=13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>10</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N=19</td>
<td>19</td>
<td>19</td>
<td>17</td>
<td>16</td>
<td>12</td>
<td>9</td>
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**Thrombin Generation**

<table>
<thead>
<tr>
<th>Days since first dose</th>
<th>1</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>180</th>
<th>270</th>
<th>360</th>
</tr>
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<tbody>
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<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>N=13</td>
<td>12</td>
<td>10</td>
<td>11</td>
<td>11</td>
<td>9</td>
<td>8</td>
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<tr>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N=17</td>
<td>17</td>
<td>17</td>
<td>15</td>
<td>13</td>
<td>12</td>
<td>7</td>
</tr>
</tbody>
</table>

*Data transfer 15 June 2017
AT, antithrombin; SEM, standard error of the mean; HV, Healthy Volunteer
†Only patients with >56 days in OLE included in analysis; patients excluded from TG analysis if they administered factor or bypassing agent within 48 hours

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Interim Fitusiran Phase 2 Open-Label Extension (OLE) Study Results*
Exploratory Analysis of Bleed Events

Summary of Median ABRs in all Patients

- 48% (16/33) of patients bleed free during observation period†
  - Overall median ABR in observation period = 1 (IQR: 0-3)
- 67% (22/33) of patients reported no spontaneous bleeds
  - Overall median AsBR in observation period = 0 (IQR: 0-2)

Summary of Median ABRs in Patients without Inhibitors

- Median duration in observation period: 13 months [range: 2 – 19]
- Mean AT activity in observation period (relative to baseline): 22%

Summary of Median ABRs in Patients with Inhibitors

- Median duration in observation period: 6 months [range: 1 – 11]
- Mean AT activity in observation period (relative to baseline): 18%

*Data transfer 15June2017
ABR, annualized bleeding rate; AsBR, annualized spontaneous bleeding rate; AT, antithrombin; PPx, prophylaxis; OD, on demand
†Observation period defined as day 29 of treatment to earlier of data transfer or 56 days after last dose

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Interim Fitusiran Phase 2 Open-Label Extension (OLE) Study Results*
Characteristics of Bleed Events During Treatment with Fitusiran

Bleed events evaluated in patients when antithrombin lowering was >75%

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients without Inhibitors (n=19)</th>
<th>Patients with Inhibitors (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bleeds, n</td>
<td>25</td>
<td>68</td>
</tr>
<tr>
<td>Patients experiencing</td>
<td></td>
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<tr>
<td>bleed(s), n</td>
<td>10</td>
<td>5</td>
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<tr>
<td>Causality</td>
<td></td>
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<tr>
<td>Spontaneous</td>
<td>8</td>
<td>50</td>
</tr>
<tr>
<td>Traumatic</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>Other†</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joint</td>
<td>19</td>
<td>54</td>
</tr>
<tr>
<td>Muscle</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>Internal</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Skin/mucosa</td>
<td>3</td>
<td>-</td>
</tr>
</tbody>
</table>

*Data transfer 15June2017
†Patient took factor treatment for abdominal pain
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Interim Fitusiran Phase 2 Open-Label Extension (OLE) Study Results*
Management of Bleed Events with Factor Replacement in Patients without Inhibitors*

<table>
<thead>
<tr>
<th>Treatment of Bleeds</th>
<th>FVIII (n=8)</th>
<th>FIX (n=2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendation from Protocol</td>
<td>No more than 30 IU/kg; re-dose after 24 hours if symptoms not relieved</td>
<td>No more than 50 IU/kg; re-dose after 24 hours if symptoms not relieved</td>
</tr>
<tr>
<td>Total bleeds, n</td>
<td>18</td>
<td>7</td>
</tr>
<tr>
<td>Total administrations, n</td>
<td>20</td>
<td>27</td>
</tr>
<tr>
<td>Mean administrations per bleed (median; range)</td>
<td>1.1 (1; 1-2)</td>
<td>3.9 (3; 1-8)</td>
</tr>
<tr>
<td>Mean dose per injection (range)</td>
<td>17 (5 – 31) IU/kg</td>
<td>18 (9 – 27) IU/kg</td>
</tr>
<tr>
<td>% using less than or same amount of factor per bleed as prior to fitusiran</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Mean total amount of factor per bleed</td>
<td>19 IU/kg</td>
<td>70 IU/kg</td>
</tr>
</tbody>
</table>

*Data transfer 15 June 2017
FVIII, factor VIII; FIX, factor IX
Replacement Factor Products Used: Advate, Aimafix, Benefix, Eloctate, Haemate, Helixate, Immunate, Immunine, Octanate, Recombinate, Refacto
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### Interim Fitusiran Phase 2 Open-Label Extension (OLE) Study Results*

Management of Bleed Events with Bypassing Agents in Patients with Inhibitors*

<table>
<thead>
<tr>
<th>Treatment of Bleeds</th>
<th>aPCC (n=4)</th>
<th>rFVIIa (n=1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendation from Protocol</strong></td>
<td>Up to 75 U/kg for minor to moderate bleeds and up to 100 U/kg (no more than 200 U/kg/day) for major bleeds at 12-hour intervals; to be continued until clear signs of clinical improvement</td>
<td>Up to 90 μg/kg every 2 hours, adjustable based on severity of bleeding until hemostasis is achieved. For severe bleeds, up to 90 μg/kg every 3-6 hours after hemostasis is achieved</td>
</tr>
<tr>
<td><strong>Total bleeds†, n</strong></td>
<td>56</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total administrations, n</strong></td>
<td>82</td>
<td>8</td>
</tr>
<tr>
<td><strong>Mean administrations per bleed (Median; range)</strong></td>
<td>1.5 (1; 1-3)</td>
<td>2.7 (3; 2-3)</td>
</tr>
<tr>
<td><strong>Mean dose per injection (range)</strong></td>
<td>27 (14 – 37) U/kg</td>
<td>59 (37 – 62) μg/kg</td>
</tr>
<tr>
<td><strong>% using less than or same amount of BPA per bleed as prior to fitusiran</strong></td>
<td>95% (53)</td>
<td>100% (3)</td>
</tr>
<tr>
<td><strong>Mean total amount of BPA used per bleed</strong></td>
<td>40 U/kg</td>
<td>156 μg/kg</td>
</tr>
</tbody>
</table>

*Data transfer 15June2017

aPCC, activated prothrombin complex concentrates; rFVIIa, Recombinant factor VIIa; BPA, bypassing agent

Bypassing agents used: FEIBA, NovoSeven

†9 bleeds treated with Prothromplex not detailed on this slide

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Interim Fitusiran Phase 2 Open-Label Extension (OLE) Study Results*

Summary

Increasing patient safety experience, with up to 20 months of dosing in Phase 2 OLE

- Majority of AEs were mild or moderate in severity; ISRs most common non-laboratory AE, all mild and transient
- No thromboembolic events; no clinical or laboratory evidence of pathologic clot formation
- Asymptomatic ALT increases >3X ULN observed in HCV Ab+ patients; most cases improved without dose interruption; 1 case led to discontinuation

Encouraging results in patients with hemophilia A and B, with and without inhibitors

- Approximately 80% AT lowering with low inter-patient variability achieved with once-monthly subcutaneous dosing
- Exploratory post-hoc analysis of bleed events demonstrates median ABR = 1 for all patients†
  - 48% (16/33) patients bleed-free and 67% (22/33) patients experiencing zero spontaneous bleeds

All bleed events in patients successfully managed with replacement factor or BPA

*Data transfer 15June2017
†During observation period; defined as day 29 of treatment to earlier of data transfer or 56 days after last dose

ABR, annualized bleeding rate; AE, adverse events; AT, antithrombin; BPA, bypassing agent; ISR, injection site reactions; SAE: serious adverse events; ULN, upper limit of normal

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Next Steps
Modeling Based on Clinical Data Supports 80 mg as Phase 3 Dose

Simulation of mean ABR as a function of AT suggests a target of ~80% AT lowering

Larger proportion of patients at 80 mg maintain target AT throughout dosing interval

Modeled Dose-AT Relationship

<table>
<thead>
<tr>
<th>% of Patients with &gt;80% AT Lowering at Steady-State</th>
<th>50 mg Monthly</th>
<th>80 mg Monthly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak</td>
<td>72</td>
<td>92</td>
</tr>
<tr>
<td>Trough</td>
<td>66</td>
<td>88</td>
</tr>
</tbody>
</table>
Next Steps
ATLAS Phase 3 Program Initiated

**ATLAS - INH**
- Adults and adolescents with hemophilia A or B with inhibitors
- Currently manage bleeds with on-demand bypassing agent therapy
- N~50
- 9 months fitusiran

**ATLAS - A/B**
- Adults and adolescents with hemophilia A or B without inhibitors
- Currently manage bleeds with on-demand (OD) factor replacement therapy
- N~100
- 9 months on-demand BPA

**ATLAS - P PX**
- Adults and adolescents with hemophilia A or B with or without inhibitors
- Currently manage bleeds prophylactically
- N~100
- 6 months PPX factor/BPA

**Primary Endpoints:**
- ABR†

**Secondary Endpoints:**
- Spontaneous ABR
- Joint ABR
- QOL (Haem-A-QOL)

Patients who complete the study may be eligible for fitusiran treatment in ATLAS-OLE study

†Powered to detect as little as a 60% reduction from control to fitusiran
‡Powered to detect as little as a 50% reduction from control to fitusiran

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Acknowledgements

Thank you to the patients, investigators, and study staff who participated in these studies

<table>
<thead>
<tr>
<th>Country</th>
<th>PI Name</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>United Kingdom</td>
<td>Steve Austin</td>
<td>London – St. George’s Healthcare NHS Trust Haemophilia Centre</td>
</tr>
<tr>
<td></td>
<td>David Bevan</td>
<td>London – The Centre for Haemostasis and Thrombosis Guy’s and St. Thomas’ Hospital</td>
</tr>
<tr>
<td></td>
<td>Desmond Creagh</td>
<td>Truro – Royal Cornwall Hospital</td>
</tr>
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<td>Charles Hay</td>
<td>Manchester – Manchester Royal Infirmary</td>
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<td></td>
<td>Tim Mant</td>
<td>London – Quintiles Drug Research Unit</td>
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<tr>
<td></td>
<td>John Pasi</td>
<td>London – The Royal London Haemophilia Centre</td>
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<tr>
<td></td>
<td>Savita Rangarajan</td>
<td>Basingstoke – North Hampshire Haemophilia Centre</td>
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<td></td>
<td>Pratima Chowdary</td>
<td>London – Royal Free Hospital Haemophilia Centre and Thrombosis Unit</td>
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<tr>
<td></td>
<td>Catherine Bagot</td>
<td>Glasgow - Glasgow Royal Infirmary Department of Haematology</td>
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<td>Bulgaria</td>
<td>Pencho Georgiev</td>
<td>Plovdiv – University Multiprofile Hospital for Active Treatment “Sveti Georgi”</td>
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<tr>
<td></td>
<td>Toshko Lissitchkov</td>
<td>Sofia - Department of Chemotherapy, Haemotherapy and Hereditary Blood Diseases at Clinical Hematology Clinic Specialized Hospital for Active Treatment of Haematological Diseases</td>
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<tr>
<td></td>
<td>Liana Gercheva-Kyuchukova</td>
<td>Varna - Clinical Hematology Clinic, Multiprofile Hospital for Active Treatment &quot;Sveta Marina&quot;</td>
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<tr>
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<td>Zurich – Universitatsspital Zurich, Klinik fur Hamatologie</td>
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<td>Brigitte Brand-Stauffer</td>
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<tr>
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<td>Margarita Timofeeva</td>
<td>Kirov - Kirov Research Institute of Hematology and Blood Transfusion</td>
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<tr>
<td>United States</td>
<td>Margaret Ragni</td>
<td>Pittsburgh - Hemophilia Center of Western Pennsylvania</td>
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