TMC435 a Second Generation HCV NS3/4A Protease Inhibitor

National Swedish Hepatitis Meeting

9 September 2010
Nordic Sea Hotel i Stockholm

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CSO, Research & Development
Medivir
TMC435 HIGHLIGHTS

- Leading next generation protease inhibitor
- Superior potency compared with first generation PIs (telaprevir, boceprevir)
- Potent anti-viral activity shown in phase 2a and 2b clinical trials
- Low pill burden: convenient one pill once daily
- No significant food interactions
- No adverse events over current SoC. There were no relevant differences between TMC435 and placebo for AEs in the 24week interim analysis of the phase2b PILLAR study
Hepatitis C

Disease and market
- Approximately 170 million worldwide chronically infected with hepatitis C virus
- Approximately 12 million infected in the US, Europe and Japan
- Estimated market value of over USD 10 billion in 2015

Medivir HCV commitment
- HCV PI – TMC435 – Tibotec/Johnson & Johnson
- HCV nucleoside NS5B inhibitor – Tibotec/Johnson & Johnson
- HCV in-house discovery programs
Hepatitis C Virus (HCV) Infection

**General background**
- *Flaviviridae* family
- Positive-sense single stranded RNA genome
- The liver is the major target site of HCV replication
- HCV does not kill the liver cells, triggers immune-mediated inflammatory response that rapidly clears the infection or slowly destroys the liver
- Leading cause of chronic liver disease as well as primary indication for liver transplantation

**Transmission routes**
- Blood contact
- Drug abusers
- Healthcare workers
- Tattooing
Prevalence and Genotypic Distribution

Genotypic distribution
- Six genotypes (1-6), >70 subgenotypes and an array of quasispecies
- Most frequent infections G1, G2, and G3
- G1a Most prevalent in US, Northern Europe, and Brazil
- G1b Most prevalent in Eastern and Southern Europe, China, and Asia
- G3 World wide distribution
- G4-5 Most frequent in Africa and Middle East (e.g. Egypt)
- G6 Most frequent in Asia
Current Treatment and Medical Need

Current treatments

- SoC: Peg-IFN, weekly injections, and ribavirin (800-1200 mg/day BID). Severe side effects such as hemolytic anemia, depression, anxiety, and fatigue and pain symptoms

  - **G1, G4 -G6: 48 weeks of treatment**
    - G1: 40-50% SVR
    - G1: Afro Americans 19-28% SVR
    - G1: HCV/HIV co-infected 29% SVR
    - G4: 55-72% SVR
    - G5:~60 %SVR

  - **G2 & G3: 24 weeks of treatment**
    - G2: 80-93% SVR
    - G3: 66-80% SVR

Current unmet medical needs

- Improved treatments for G1 patients (naïve and treatment experienced)
  - Increased SVR
  - Shorter treatments
  - Improved tolerability
  - Higher compliance
    - PO dosing, lower drug burden and simplified dosing (once daily, no food interaction and large “forgiveness” factor)

- Effective treatments for HCV/HIV co-infected and non-Caucasian patients
Overview of Anti-HCV Therapies in Development

- New interferon & ribavirin analogues
- Immune modulators (non-interferon)
- Small molecule Directly Acting Antiviral (DAA) agents
- Therapeutic vaccines

Schinazi R,F et al. J. Viral Hepatitis., 2010, 17, 77
DAA Agents - Key Characteristics

**NS3 /4A Inhibitors**
- High potency
- Multi-genotypic coverage
- Intermediate barrier to resistance

**NS5A Inhibitors**
- High potency
- Multi-genotypic coverage
- Unknown- likely intermediate barrier to resistance

**NS5B Nucleoside Inhibitors (NI)**
- Intermediate potency
- Pan genotypic coverage
- High barrier to resistance
- Often correlated with potential safety issues

**NS5B Non Nucleoside Inhibitors (NNI)**
- Intermediate potency
- Limited-genotypic coverage
- Low barrier to resistance
Early studies showed that the NS3 protease was inhibited by a hexapeptide (N-terminal) produced by cleavage of NS5A/5B.

Inhibitor design features leading up to TMC435:
- Novel P2 motifs developed and validated into potent drug-like inhibitors - differentiation
  - A novel P2 cyclopentane-dicarboxylic acid unique to the HCV NS3 protease inhibitor field
- Truncation of the P4 group possible with new P2 template - differentiation
  - Less sensitive to mutations in the S4 pocket
  - Other HCV NS3 protease inhibitor developed need employ P4 groups
- Macro cyclic structure
- Acid P1 bioisostere

Novel P2 proline mimetics developed - unique to the field

P2 substituted proline

1 (NS5A/NS5B product)
NS3 \(Ki = 71 \, \mu\text{M}\)
X-ray structure of TMC435 in complex with HCV NS3 protease

- NS3-1b (BK aa1-181) co-crystallized with 23-mer NS4A
- Resolution of 2.4 Å
TMC435 a Potent HCV NS3/4A Inhibitor

**In vitro Profile**
- Reversible NS3A protease inhibitor
- Enzymatic assay: $K_i (G1a) = 0.4 \text{ nM}$; $K_i (G1b) = 0.5 \text{ nM}$
- High selectivity over selected human proteases $>1,000$ (including HNE)
- $EC_{50} = 8 \text{ nM}$ in genotype 1 replicon
- Minimal impact of functional protein binding ($\sim 2$ FC of $EC_{50}$)
- Selectivity Index (SI) = $CC_{50}/EC_{50}$ across many cell lines $>1250$
- Synergistic with IFN-α and a NS5B inhibitor; additive with RBV

**In vivo Preclinical Profile**
- High oral bioavailability in several species: 45-80%
- High liver to plasma ratio: $\sim 40$

Two classes of NS3/4A protease inhibitors in clinical development

First generation HCV PIs

Covalent reversible binding,
ketooamide linear inhibitors

Telaprevir
(VX-950; Phase 3)

Boceprevir
(SCH 503034; Phase 3)

Non-covalent reversible binding

TMC435, (Phase 2b)

Danoprevir, ITMN-191, RG7227 (Phase 2)

Bi201335 (Phase 2b)

Vaniprevir, MK-7009 (Phase 2b)
Hepatitis C – the competitive landscape

<table>
<thead>
<tr>
<th>Pre-clinical</th>
<th>Phase 1a</th>
<th>Phase 1b</th>
<th>Phase 2a</th>
<th>Phase 2b</th>
<th>Phase 3</th>
</tr>
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<tbody>
<tr>
<td>Intermune</td>
<td>VPY-376</td>
<td>ACH-1625</td>
<td>Danoprevir ITMN-191</td>
<td>TMC435</td>
<td>Telaprevir VX-950</td>
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<tr>
<td>Taigen</td>
<td>PHX1766</td>
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<td>ABT-450</td>
<td>BI201335</td>
<td>Boceprevir SCH-503034</td>
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<tr>
<td>Novartis</td>
<td>IDX320</td>
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<td>BMS-650032</td>
<td>Vaniprevir MK-7009</td>
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<tr>
<td>Vertex</td>
<td>MK-5172</td>
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<td>GS-9256</td>
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<tr>
<td>AVL-181,192</td>
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<td>ACH-2684</td>
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**HCV PI’s in combination with SoC**

- Combinations of DAA agents:
  - Telaprevir in phase 2a in combination with VX-222 (NNRTI) +/- SoC
  - Danoprevir in phase 2a in combination with RG7128 (NI) +/- SoC
  - BMS-650032 in phase 2a in combination with BMS-790052 (NS5A inh) +/- SoC
  - GS-9256 in combination with GS-9190 (NNRTI) +/- Ribavirin
- Danoprevir and ABT-450 employ ritonavir-boosting
PK profile in healthy volunteers after single and repeated dosing

TMC435 was safe and well-tolerated in the study, when given to HCV-negative healthy volunteers at single oral doses up to 600 mg and at 5 days of oral doses up to 400 mg once-daily.

The pharmacokinetic profile of TMC435 supports once-daily dosing.

No dose-dependent increase in AE incidence was observed.
Median change from baseline HCV RNA in treatment experienced patients (n = 6) treated with TMC435 (monotherapy)

- Five-day treatment with TMC435 200 mg QD resulted in a maximal median decrease in HCV viral load of 3.9 Log_{10} IU/mL (range 2.9 - 4.1 Log_{10} IU/mL) observed at day 6
- No difference in response between genotype 1a and 1b
- No viral breakthrough observed
TMC435 C201 Phase IIa study:
Cohorts 1 and 2 in treatment-naïve and cohorts 4 and 5 in treatment-experienced, genotype-1 HCV-infected patients

The planned Cohort 3 was cancelled prior to the initiation of treatment.
Patients are followed-up for 24 weeks after end of treatment to assess SVR rate:
PEGIFNα-2a, pegylated Interferon α-2a
RBV, ribavirin
SVR, sustained virologic response
TMC435: Cohorts 1 and 2 in treatment-naïve HCV-infected patients
- Potent Antiviral Activity at week 4 and at week 12

Panel A, Week 4

Panel B, Week 4

- In Panel B at Week 12, 9/9 patients (100%) in the 75 mg arm and 10/10 patients (100%) in the 200 mg arm had HCV RNA <10 IU/mL, i.e. below limit of detection) (Week 12 = 4-weeks of TMC435/SoC plus 8-weeks of SoC alone)
TMC435 C201 Phase 2a study:
Cohorts 1 and 2 in treatment-naive and cohorts 4 and 5 in treatment-experienced, genotype-1 HCV-infected patients
(22%), 5/9 (56%) and 3/10 (30%) patients in 75, 150 and the 200 mg groups reached undetectable levels (< 10 IU/mL) after 4 weeks of treatment, compared to 0/9 patients on placebo.
TMC435 C201 Phase 2a study:
Cohorts 1 and 2 in treatment-naïve and cohorts 4 and 5 in treatment-experienced, G1 HCV-infected patients
Antiviral activity and safety of TMC435 combined with pegylated interferon and ribavirin in hepatitis C patients with genotype 1 who had previous exposure to TMC435

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1 Academic Medical Center, Amsterdam, The Netherlands; 2 Tibotec BVBA, Mechelen, Belgium; 2 Tibotec Inc., Yardley, PA, USA

OPERA-1 is a Phase IIa double-blind, randomized, placebo-controlled trial investigating different doses of TMC435 in both treatment-naive and treatment-experienced patients across multiple cohorts. Cohort 5 comprised prior non-responders and relapsers to interferon (IFN)-based therapy who had previously received 5 days of monotherapy with TMC435 200 mg once daily (QD) in a Phase Ib trial (Study C101).

Four out of five patients completed triple therapy with TMC435 200 mg QD whilst one patient discontinued due to increased blood bilirubin. At Day 28, all four patients who completed treatment achieved HCV RNA <25 IU/mL with an overall mean change from baseline of 5.86 log10 IU/mL. Three of those four patients had HCV RNA below the lower limit of detection (<10 IU/mL) at Day 28.

No viral breakthroughs (defined as >1 log10 IU/mL increase from nadir in HCV RNA) were observed within 4 weeks.

The most common adverse event (AE) during triple therapy was influenza-like illness (n=4). There were no serious AEs.

ALT and AST levels decreased over the 4-week treatment period. Other than an increase in bilirubin, no clinically relevant changes were observed in any other laboratory parameters, ECG parameters, or vital signs.

Presented at AASLD, Boston, MA, USA, October 30-November 3, 2009
### TMC435 Opera-1 (C201)

#### Trial design and results

- **Once daily** (q.d.) treatment of TMC435 in doses from 25 to 200 mg + SoC
- **Four-week triple therapy** (RVR), followed by SoC alone up to week 24 or 48
- **In treatment-naïve patients**, potent antiviral activity was achieved at week 4 (RVR) and at week 12 (EVR)
  - At week four 8/9 and 7/10 patients were undetectable in the 75 and 200 mg groups respectively (Panel B)
  - At week 12 all of the patients in the once daily 75 mg and 200 mg arms (Panel B) had HCV RNA <10 IU/mL (undetectable)
- **In treatment-experienced patients** potent antiviral activity was achieved at week 4 (RVR)
  - 7/9 patients levels below LLQ (<25 IU/mL) at 150 mg and 8/10 for 200 mg at day 28

#### Conclusions

- Demonstrated potent antiviral activity
- Was generally safe and well tolerated
- Was not associated with adverse event-related treatment discontinuations
- Mild and reversible increases in bilirubin was observed. This was mainly observed in the highest dose groups (200 mg), whereas the highest dose in the ongoing phase 2b studies is 150 mg. The mechanism of action has been determined and will be presented at an upcoming conference
- No evidence of any drug-related hepatotoxicity
# TMC435 clinical trial overview

<table>
<thead>
<tr>
<th>Phase 1 studies</th>
<th>Phase 2a studies</th>
<th>Phase 2b studies ongoing</th>
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</thead>
<tbody>
<tr>
<td>Extensive drug-drug interaction program ongoing with commonly used drugs</td>
<td>Opera-1 (C201)</td>
<td>PILLAR (C205) – genotype-1 infected treatment-naïve patients</td>
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<td>DRAGON (C215) – genotype-1 infected treatment-naïve Japanese patients</td>
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<td>ASPIRE (C206) – genotype-1 infected treatment-experienced patients</td>
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<td>Opera-2 (C202)</td>
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**Opera-1 (C201)**
- 4-week antiviral activity, safety and PK data available
- TMC435 shows potent antiviral activity and was well tolerated in treatment-naïve and treatment-experienced patients with genotype-1 HCV infection
- Doses between 75 and 150 mg selected for phase 2b

**Opera-2 (C202)**
- PoC study in patients with non-genotype-1 HCV infection – completed
**TMC435 – Ongoing phase 2 clinical trials**

<table>
<thead>
<tr>
<th>DRAGON (C215) – Trial design and results</th>
<th>Opera-2 (C202) – Trial design and results</th>
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<tbody>
<tr>
<td><strong>Japanese phase 2b study in treatment-naïve genotype-1 HCV patients</strong></td>
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<tr>
<td>▪ TMC435-C215 is a Japan phase 2b study in 92 genotype-1 treatment-naïve patients</td>
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<tr>
<td>▪ Study start date: June 2009</td>
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<tr>
<td>▪ Patients received TMC435 (50 mg or 100 mg) for a duration of 12 or 24 weeks</td>
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<tr>
<td>▪ In treatment arms 1 and 2, subjects received 12 weeks of triple therapy with TMC435 once daily plus SoC followed by 12 weeks of treatment with SoC</td>
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<tr>
<td>▪ In treatment arms 3 and 4, patients received 24 weeks of triple therapy with TMC435 once daily plus SoC</td>
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<tr>
<td>▪ In treatment arm 5 (control group), patients will be treated with SoC treatment for 48 weeks</td>
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<tr>
<td><strong>Phase 2a PoC study in treatment-naïve genotype 2 to 6 HCV patients</strong></td>
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<tr>
<td>▪ Study start date: February 2009</td>
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<tr>
<td>▪ Study completion date: November 2009</td>
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<tr>
<td>▪ Patients received TMC435 during seven days, once daily dosing at 200 mg, as monotherapy. Subsequently, they continued with SoC treatment consisting of pegylated interferon and ribavirin upon agreement with the study doctor</td>
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</table>
TMC435 phase 2b trial design

**PILLAR (C205)**
- TMC435-C205 is a global phase 2b study in 386 genotype-1 treatment-naïve patients
- Study start date: May 2009
- Once daily (q.d.), 75 mg and 150 mg, of TMC435 + SoC:
  - 12-week triple therapy followed by SoC alone up to week 24
  - 24-week triple therapy

**ASPIRE (C206)**
- TMC435-C206 is a global phase 2b study in 457 genotype-1 treatment-experienced patients
- Study start date: September 2009
- Once daily (q.d.), 100 mg and 150 mg, of TMC435 + SoC:
  - 12-week triple therapy followed by 36 weeks of SoC
  - 24-week triple therapy followed by 24 weeks of SoC
  - 48-week triple therapy

**Primary endpoint:** Proportion of patients with undetectable virus levels at Week 72

**SoC:** Ribavirin 1,000-1,200 mg BID + pegIFNalpha-2A 180 μg weekly

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**Medivir**

National Swedish Hepatitis Meeting
9 September 2010, Stockholm
Press Release on 12 July 2010
TMC435-C205 PILLAR Phase 2b study:
24-week Interim Results in 386 Treatment-naïve HCV Patients

- 83% of patients were able to stop all therapy at Week 24 in TMC435 treatment groups
  - Response guided design in TMC435-C205 PILLAR Phase 2b study
  - Patients stopped all treatment at week 24 if HCV RNA levels at week 4 were < 25 IU/mL detectable or undetectable and HCV RNA levels at week 12, week 16 and week 20 were < 25 IU/mL undetectable. Patients who did not meet the above response-guided criteria continued with SOC until week 48
- Potent and consistent antiviral efficacy was demonstrated at 24-week end-of-treatment
- Interim SVR4 and SVR12 data:
  - SVR4 and SVR12 data, at the time point of the interim analysis, were available for 82% and 42% of the TMC435-treated patients respectively who had stopped all therapy before or at Week 24 and had completed the follow-up visits
  - For the interim SVR4 and SVR12 rates there were no major differences between TMC435 doses or length of triple therapy
  - 92% of patients taking TMC435 and Peg-IFN/RBV (SoC) achieved undetectable HCV RNA levels at week 4 and 92% at week 12 after cessation of treatment, i.e. SVR4 and SVR12
- Both the viral breakthrough rate (4.9%) and relapse rate (1.6%) were low in the TMC435 treatment groups.
## Virologic Response Overview - Trial C205 (Week 24 Interim Analysis)

### ITT Population, Frequency of Undetectable* HCV RNA Levels During and After Treatment

<table>
<thead>
<tr>
<th>Treatment week</th>
<th>TMC12PR24 75mg q.d.</th>
<th>TMC24PR24 75mg q.d.</th>
<th>TMC12PR24 150mg q.d.</th>
<th>TMC24PR24 150mg q.d.</th>
<th>SoC</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>N=78</td>
<td>N=75</td>
<td>N=77</td>
<td>N=79</td>
<td>N=77</td>
</tr>
<tr>
<td>Week-24, EoT***</td>
<td>67/73 (92%)</td>
<td>65/67 (97%)</td>
<td>68/74 (92%)</td>
<td>73/78 (94%)</td>
<td>4/18 (22%)**</td>
</tr>
</tbody>
</table>

### Follow-up at Week-4 and Week-12 after EoT

<table>
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<tr>
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<th>SVR4 59/65 (91%)</th>
<th>56/60 (93%)</th>
<th>57/61 (93%)</th>
<th>63/68 (93%)</th>
<th>NA****</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR12</td>
<td>32/33 (97%)</td>
<td>27/29 (93%)</td>
<td>32/36 (89%)</td>
<td>29/32 (91%)</td>
<td>NA</td>
</tr>
</tbody>
</table>

* < 25 IU/mL undetectable
** End of treatment
***EoT: End of Treatment
**** Patients in the control arm continue SoC till Week 48 and SVR data are not available
q.d.: once daily, PR: pegIFNalpha-2A and ribavirin
SVR4: undetectable HCV RNA at EoT & undetectable HCV RNA 4 weeks after planned EoT
SVR12: undetectable HCV RNA at EoT & undetectable HCV RNA 12 weeks after planned EoT
TMC435 was well tolerated at all doses and regimens studied.
- TMC435 was generally safe and well tolerated with no relevant differences in adverse events (AEs) between placebo and TMC435 treatment groups. Most AEs were mild to moderate in severity and the discontinuation rate due to AEs was low and not different from placebo.

Type and incidence of adverse events (AEs) were similar across all treatment groups.
- When looking at particular adverse events of interest, the incidence of rash, pruritis, GI side effects and anemia were similar in TMC435 groups and placebo and were generally mild to moderate in nature.

In laboratory parameters, there were no clinically relevant differences between any TMC435 groups and placebo except for mild bilirubin elevations.
- Mild increases in bilirubin (total, direct and indirect) were observed in the TMC435 150-mg dose groups. This pattern of mild, non-progressive, rapidly reversible bilirubin elevations which are not associated with abnormalities in other hepatic parameters is consistent with the underlying mechanism of a benign competitive inhibition of biliary transporter systems in the hepatocyte.

Significant decreases in transaminases (ALT and AST) were observed in all treatment groups.

Further safety and virology data will be presented at the upcoming AASLD meeting in October 2010.
TMC435 news flow 2010

Events in the next 6 months

- **DRAGON (C215)**
  - Presentation of 12 week interim data from the phase 2b study in treatment-naïve Japanese genotype-1 HCV patients

- **PILLAR (C205)**
  - Presentation of top-line 24 week interim data at the AASLD meeting in Boston
  - 48 week end of treatment data available in 4Q10

- **Opera-2 (C202)**
  - Presentation of data from the phase 2a study in treatment-naïve genotype 2–6 HCV patients at the AASLD meeting in Boston

- **Presentation of mechanism of action (MOA) behind the transient reversible increases in bilirubin**
  - The AASLD meeting in Boston

- **ASPIRE (C206)**
  - Top-line 24 Week interim data from the phase 2b study in treatment-experienced genotype-1 HCV patients available in 4Q10

- **Phase 3**
  - Start of phase 3 in treatment-naïve genotype-1 HCV patients
**Hepatitis C**

The future of new DAA agents – new treatments evolving

- **Directly Acting Antiviral (DAA) agents**
  - New DAA agents will dramatically increase SVR, shorten treatment duration and minimize development of resistance
  - DDA agents with different MOA will initially be used as “add-on” therapy but will in combinations eventually displace one or both of ribavirin and Peg-IFN
  - Combinations of a Protease Inhibitor with other direct antivirals will drive the future market
  - TMC435, as a front runner of this new wave, is strongly positioned to become an integral part of these future DAA combination treatments

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Gregory Fanning
Khalid Abou Farha
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TMC435 global development
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Vanitha Sekar
Monika Peeters

The patients and their families