*A research based specialty pharmaceutical company focused on infectious diseases*

**November 2011**

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# Commercializing TMC435 – Our Core Product

- Favorable safety profile: comparable with placebo in phase IIb clinical trials
- Excellent anti-viral efficacy shown in phase IIb program
- High convenience: one-pill, once-daily treatment
- Broad regulatory filing in H1-2013: all Phase III clinical trials fully enrolled

# TMC435 – Abstracts presented at the AASLD Nov 2011

**Oral Late Breaking**
**LB-5.** “TMC435 in combination with peginterferon and ribavirin in treatment-naïve HCV genotype 1 patients: Final analysis of the PILLAR Phase IIb study.

**Poster presentations:**
**1329**. “TMC435 in combination with peginterferon alpha-2a/ribavirin in treatment-naïve patients infected with HCV genotype 1: virology analysis of the PILLAR study”.

**1354**. “The pharmacokinetic interaction between the investigational HCV NS3/4A protease inhibitor TMC435 and escitalopram”.

**1353**. “The pharmacokinetic interaction between the investigational NS3-4A HCV protease inhibitor TMC435 and methadone”.

# Medivir comittment to build a leadership position in Hepatitis C

- **NS3A protease inhibitor -** TMC435, a potent, once-daily oral PI with broad genotypic coverage (1,2,4,5 and 6)
  - Broad global clinical development program ongoing:
    - In phase III for genotype 1 infected patients
    - IFN-free combinations with DAA agents initiated and in planning phase
- **NS5B -** nucleoside/nucleotide inhibitor programs
  - A nucleoside in phase Ib clinical development (TMC649128)
  - Nucleotides in preclinical development

Johnson&Johnson tibotec

  - NS5B nucleotide program – new agents in preclinical phase
- **NS5A program -** A next generation replication complex inhibitor in preclinical phase

**In-house/ unpartnered**

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# TMC435 – Broad clinical development program in genotype 1 infected HCV patients

## Phase IIb
**Reporting phase**

**PILLAR (C205)** (n=386)
Genotype-1 infected treatment-naïve patients

**DRAGON (C215)** (n=92)
Genotype-1 infected treatment-naïve patients in Japan

**ASPIRE (C206)** (n=462)
Genotype-1 infected treatment-experienced patients

## Phase III
**Fully enrolled (Aug 2011)**

**QUEST 1 (C208)** n=375
Genotype-1 infected treatment-naïve patients

**QUEST 2 (C216)** n=375
Genotype-1 infected treatment-naïve patients

**PROMISE (C3007)** 375
Genotype-1 infected *relapsed* patients

**Japan phase III program**

Genotype-1 infected *naïve and treatment experienced* patients

## IFN free combinations

**TMC435 and TMC647055,** a non-nucleoside NS5B inhibitor developed by Tibotec Pharmaceuticals

**TMC435 and PSI-7977,** a nucleotide NS5B inhibitor. A Phase II, interferon-free, 12 or 24 weeks, +/- ribavirin PoC study in genotype-1 prior null responders

**Others to be communicated**

**Broad regulatory filings anticipated H1-2013**

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For additional information please see www.clinicaltrials.gov

# TMC435 in Combination with Peginterferon and Ribavirin in Treatment-naïve HCV Genotype 1 Patients

## Final Analysis of the PILLAR Phase IIb Study (TMC435-C205)

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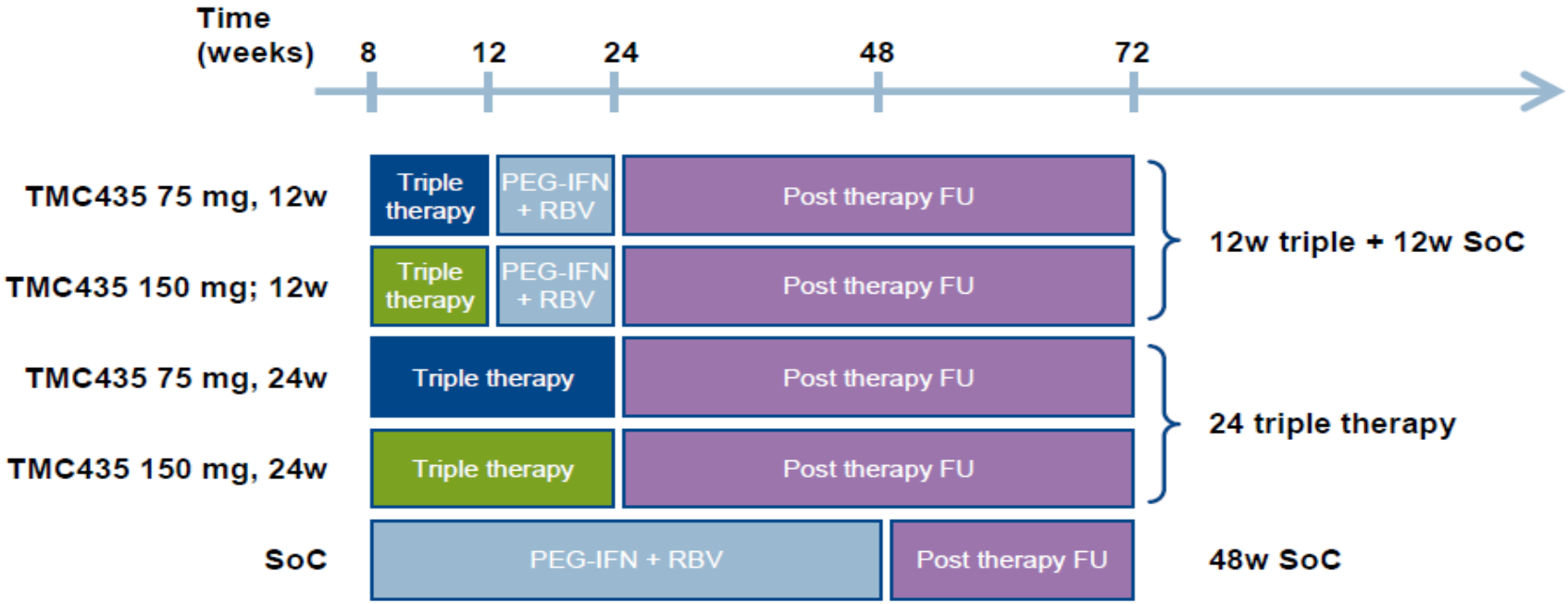
# TMC435 Phase IIb (PILLAR) in treatment naïve patients *- study design*

- **386 genotype-1 treatment-naïve** patients
- **Once daily TMC435 (75 or 150 mg**) was added to PegIFN/RBV for **12 or 24 weeks**
- **Response-guided treatment** (RGT) duration in TMC435 arms:
  - End treatment at Week 24, if HCV RNA <25 IU/mL detectable or undetectable at Week 4, *and* HCV RNA <25 IU/mL undetectable at Weeks 12, 16, and 20
  - All other patients continued PegIFN/RBV for up to 48 weeks



# TMC435 Phase IIb (PILLAR) in treatment naïve patients *- efficacy results*

| Response % (n/N) | TMC435 150 mg 12W P/R RGT N=77 | TMC435 150 mg 24W P/R RGT N=79 | Placebo 48W P/R N=77 |
|---|---|---|---|
| RVR[1] | 75(58/77) | 75 (59/79) | 5.2 (4/77) |
| EOT[2] | 92 (71/77) | 94 (74/79) | 79 (61/77) |
| SVR24[3] | 81 (62/77)* | 86 (68/79)** | 65 (50/77) |
| Viral relapse | 8.7 (6/69) | 8.0 (6/75) | 18 (11/62) |

** p<0.05, **p<0.005, significant difference versus placebo control; RGT: Response guided treatment; P/R, peginterferon ·-2a + ribavirin*
*HCV RNA <25 IU/mL undetectable at: [1]Week 4 (rapid virologic response); [2]End of treatment; [3]24 weeks after planned end of treatment;*

- **SVR24 rates of 81-86% in patients receiving 150 mg TMC435**
- **79-86% of patients eligible to receive shortened treatment duration (24w)**

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# TMC435 Phase IIb (PILLAR) in treatment naïve patients
## *- safety & tolerability results*

| Number of subjects with AE: n (%) | All TMC435 N=309 | Pbo/P/R 48W N=77 |
|---|---|---|
| AE leading to permanent stop of TMC435/Pbo & PegIFN/RBV | 11 (3.6) | 4 (5.2) |
| Grade 3 or 4 AE | 99 (32.0) | 27 (35.1) |
| Serious AE | 20 (6.5) | 10 (13.0) |
| Five most common AEs | | |
| Fatigue | 131 (42.4) | 37 (48.1) |
| Influenza-like illness | 98 (31.7) | 29 (37.7) |
| Pruritus | 96 (31.1) | 35 (45.5) |
| Headache | 142 (46.0) | 40 (51.9) |
| Nausea | 86 (27.8) | 21 (27.3) |
| AEs of interest | | |
| Rash (any type) | 65 (21.0) | 18 (23.4) |
| Anemia | 63 (20.4) | 16 (20.8) |
| Neutropenia | 75 (24.3) | 16 (20.8) |

No difference in incidence of AEs or discontinuations due to AEs between TMC435 and placebo groups

Incidence of rash, anemia, and neutropenia similar with TMC435 or placebo

**TMC435 was safe and well tolerated at all doses and durations**

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AE, adverse event; RGT, response-guided treatment

# TMC435 Phase IIb (PILLAR) in treatment naïve patients *- summary*

- ✓ **81-86% of patients achieved SVR24** with TMC435 150 mg
- ✓ **79-86% of patients** received shortened treatment duration of 24 weeks based on RGT criteria
  - Of these, **93-96% achieved SVR24** with TMC435 150 mg
- ✓ TMC435 was safe and well tolerated

**PILLAR data will support broad regulatory filing in H1 2013 for G1 HCV infected patients for TMC435 150 mg (QD)**

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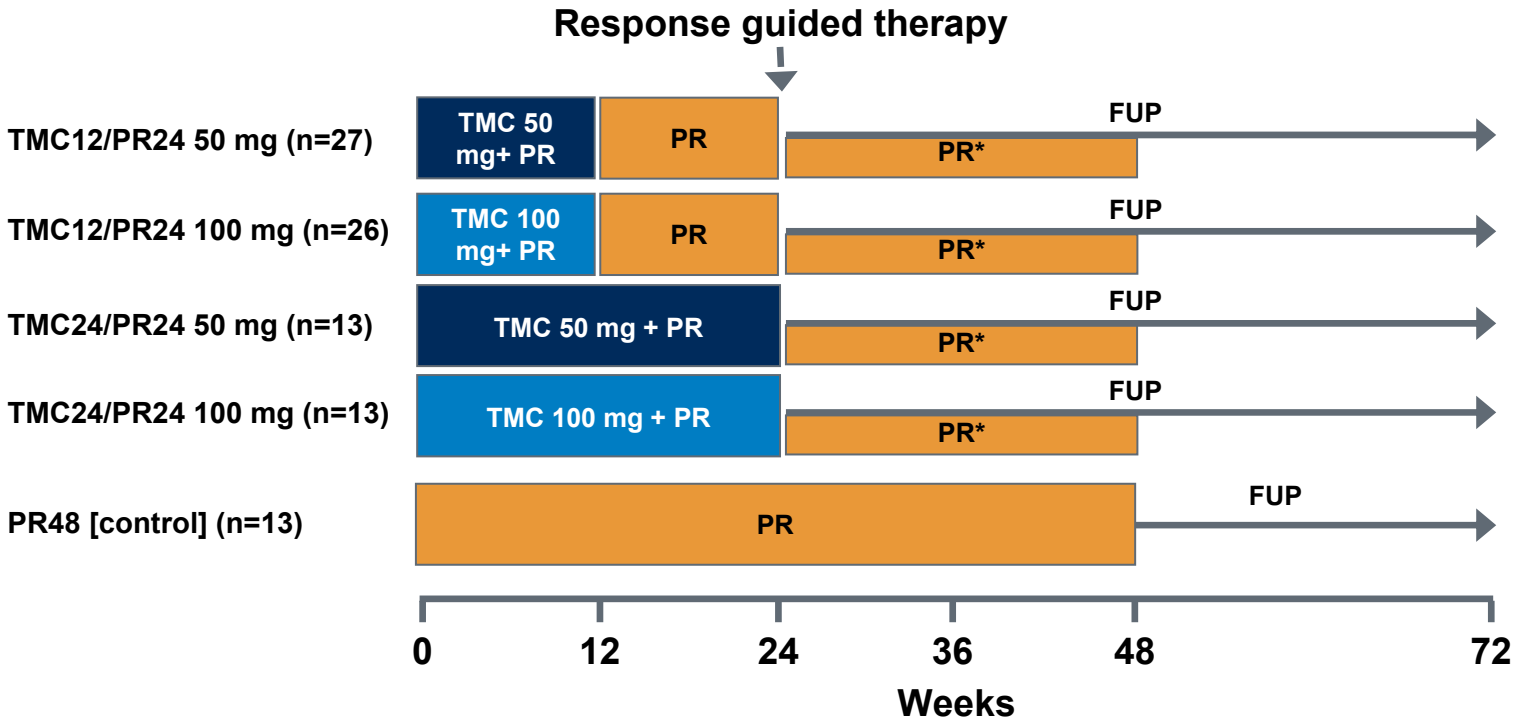
# TMC435 Phase IIb (DRAGON) in treatment naïve patients *- study design*

- Randomized, open-label, five-arm controlled trial to evaluate the efficacy, safety and PK of TMC435 (QD) in combination with pegIFNa-2a and RBV
- Genotype I infected treatment-naïve **Japanese** patients (n=92)

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# TMC435 Phase IIb (DRAGON) in treatment naïve patients *- study design*

- ✓ **82% of patients achieved SVR24** in the 100 mg TMC435 versus 46 % in the placebo control group
- ✓ **87% of patients received shortened treatment** duration of 24 weeks based on RGT criteria,
- ✓ TMC435 was safe and well tolerated

**Phase III clinical trials well underway in Japan (fully enrolled) in both treatment naïve and treatment experienced patients**

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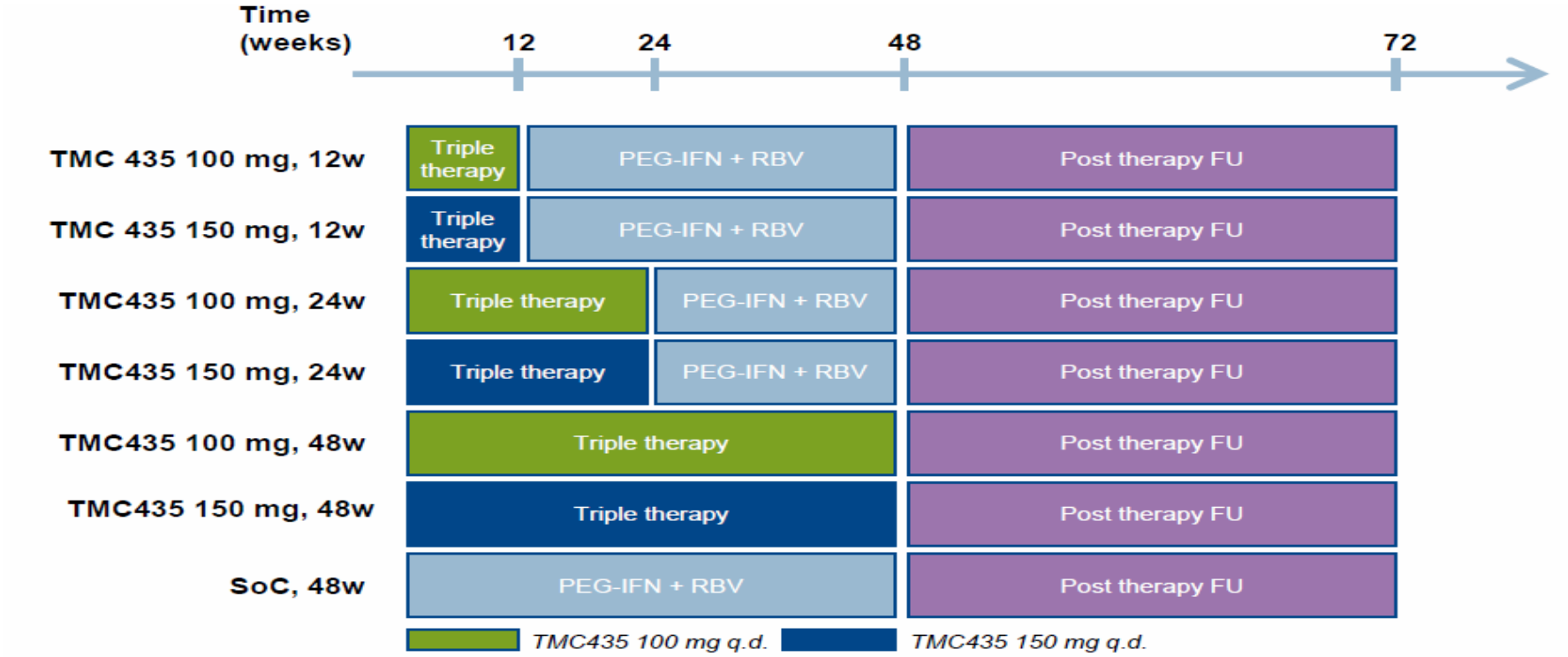
# TMC435 Phase IIb ASPIRE study in genotype 1 treatment experienced patients* - *study design*

- 462 genotype-1 relapser, partial- and null responder patients
- TMC435 was given once daily (QD) at a dose of either 100 mg or 150 mg for 12, 24, or 48 weeks in combination with 48 weeks of PegIFN/RBV.




*62 % of patients (287/462) had advanced liver disease (Metavir F2-F4)

# TMC435 Phase IIb ASPIRE study in genotype 1 treatment experienced patients* - *results*

| Virologic Response Rates (SVR24) in TMC435 Dose Groups (150 mg q.d.) vs placebo | | | | | |
|---|---|---|---|---|---|
| % (n/N) | TMC435 **12w** PR48 N=66 | TMC435 **24w** PR48 N=68 | TMC435 **48w** PR48 N=65 | **All TMC435** PR48 N=199 | **Placebo** PR48 N=66 |
| **Prior Relapser** | 77 (20/26) | 89 (24/27) | 89 (23/26) | **85** (67/79) | **37** (10/27) |
| **Prior Partial Responder** | 65 (15/23) | 75 (18/24) | 86 (19/22) | **75** (52/69) | **9** (2/23) |
| **Prior Null Responder** | 53 (9/17) | 41 (7/17) | 59 (10/17) | **51** (26/51) | **19** (3/16) |

- **High SVR24 rates in the very difficult to treat prior partial and null responders**
- **TMC435 was safe and well tolerated**
- **Phase III trial in partial and null responders in planning phase**

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*62 % of patients (287/462) had advanced liver disease (Metavir F2-F4)

# TMC435 Phase IIb program in genotype 1 patients
## *– summary concluded studies*

**TMC435 added once daily to PegIFN/RBV treatment:**

- **Was safe and well tolerated**
- **Showed excellent efficacy**

| Study | Patient population | SVR24 | 24 w treatment (RGT) |
|---|---|---|---|
| **PILLAR** | Treatment naive | **81 - 86%** | **79 - 86%** |
| **DRAGON** | Treatment naive (Japan) | **82%** | **87%** |
| **ASPIRE** | Relapsers | **85%** | - |
| **ASPIRE** | Partial responders | **75%** | - |
| **ASPIRE** | Null responders | **51%** | - |

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# TMC435 – Status and regulatory plans in genotype 1 infected patients

**For the regulatory filing the ongoing and concluded clinical trials will provide:**

- Pivotal phase III data in treatment naïve and prior relapser patients (QUEST1, QUEST2 and PROMISE)
- Phase III data in treatment naïve *and* treatment-experienced patients in Japan
- Phase IIb data in prior partial and null responders (ASPIRE)
- A large safety database

**Regulatory filing for the treatment of HCV genotype 1 infected patients anticipated H1-2013**

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