

Breakfast Meeting in Boston 2 Nov 2010

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# **Key Highlights**



Strong presence in hepatitis C building a portfolio of drug projects - TMC435 is the frontrunner in our portfolio, potentially the best in class protease inhibitor and a future blockbuster



Xerclear<sup>™</sup> / Xerese<sup>™</sup> has a unique indication text and will be a major step towards becoming a profitable research-based pharmaceutical company. Our partner GSK will market it OTC in Europe and Meda will market it Rx in North America



Strong pipeline with many potential blockbuster drugs in development with leading pharma partners. Evaluation of new programs in infectious diseases ongoing, including new HCV targets



# TMC435 – the leading next generation protease inhibitor



 Superior potency compared with first generation Pls (telaprevir, boceprevir)

 Excellent anti-viral activity shown in phase 2b PILLAR study

 Strong safety profile: no adverse events over SoC in the phase 2b PILLAR study

High convenience: one pill once daily



# Our first approved product - Xerclear™/Xerese™

#### **Overview**

- Patented combination of 5% acyclovir and 1% hydrocortisone in Medivir's proprietary cream formulation
- Market opportunity
  - 7% of the Western population, or 60 million people, suffer from severe labial herpes
  - Approved therapies offer poor results opportunity to grow the existing market
  - Limited development of current products on the market
- North America Partner with Meda
  - Prescription (Rx) status for all antiviral treatments (acyclovir, penciclovir)
  - Main competitors are Zovirax, Denavir and Abreva
- EU
  - Market dominated by OTC products

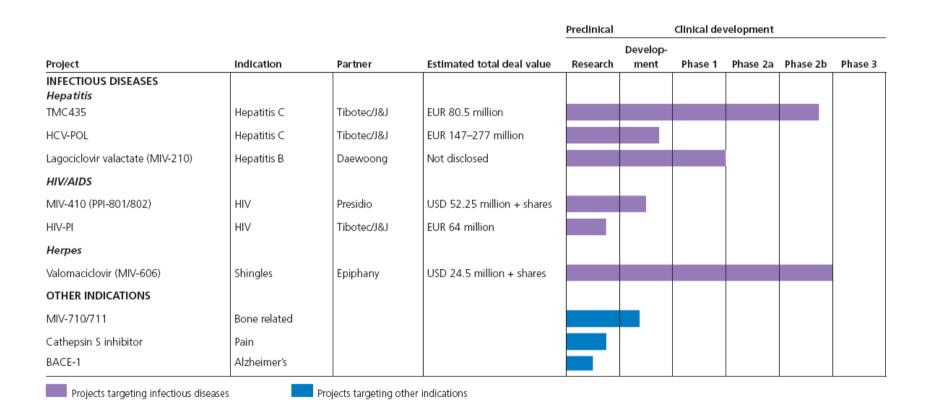
#### Launch status

- Nordic region Medivir
  - Xerclear™ launched Rx in Sweden and Finland
- North America Meda
  - Product launch in the US confirmed to Q1 2011
  - Xerese™ will be Rx in the US market
- EU and Russia GSK
  - Product launch starting summer 2011 including Sweden and Denmark as OTC
  - Initially OTC and Rx, with a switch to OTC over time
- Rest of World
  - Distribution partnerships, Daewoong I South Korea and Luxembourg Pharmaceuticals in Israel. Other territorial discussions are ongoing



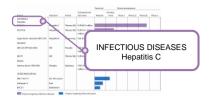


# Strong pipeline with leading pharma partners



Best-in-class protease and polymerase platform





# **Hepatitis C**

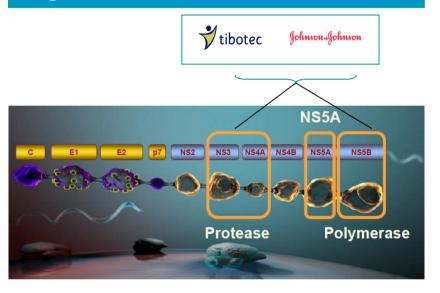
#### Disease and market

- 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 ongoing

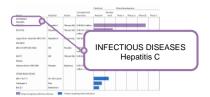
### **Programs in collaboration with**



In-house HCV programs

### **Broad commitment in HCV**





# **Hepatitis C – HCV-POL**





#### **Status**

- Partnership entered with
   Tibotec/Johnson & Johnson in May 2008
- In late preclinical development phase, broad range of activities completed, evaluation work ongoing
- Synergy shown with both TMC435 and nonnucleoside NS5B inhibitors (DAA agents)
- An ideal DAA agent for future TMC435 combination regimens

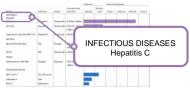
# Nucleoside/nucleotide NS5B polymerase inhibitor characteristics

- Nucleoside/nucleotide inhibitors are chainterminators
- High in vivo potency demonstrated
- Wide genotype coverage
- High barrier to resistance
- Five nucleoside/nucleotide analogues in clinical development (phase 1 and 2)

#### **Events in coming 12 month - HCV Pol**

- Start of phase 1 clinical trials
- Presentation of phase 1 clinical trial data
- Presentation on antiviral potency, mechanism of action and DAA synergy data

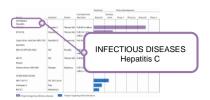




# Hepatitis C PI – the competitive landscape

Pre-clinical	Phase 1a	Phase 1b	Phase 2a	Phase 2b	Phase 3		
Intermune	VPY-376	ACH-1625	Danoprevir R-7227	TMC435	Telaprevir VX-950		
Taigen	PHX1766		ABT-450	BI201335	Boceprevir SCH-503034		
Novartis	IDX320		BMS-650032	Vaniprevir MK-7009			
Vertex	MK-5172		GS-9256				
AVL-181,192			HCV Pl's in c	ombination with	DAAs and SoC		
ACH-2684			<ul> <li>Combinations of DAA agents:         <ul> <li>Telaprevir in phase 2a in combination with VX-222 (NNRTI) +/- SoC</li> <li>Danoprevir in phase 2a in combination with R7128 (NI) +/- SoC</li> </ul> </li> <li>BMS-650032 in phase 2a in combination with BMS-790052 (NS5A inh) +/- SoC</li> <li>GS-9256 in combination with GS-9190 (NNRTI) +/- Ribavarin</li> </ul>				
			Note: nanoprevir and ABT-450 require ritonavir-boosting				





### TMC435 clinical trial overview

#### Phase 1 studies

 Extensive drug-drug interaction program ongoing with commonly used drugs

#### Phase 2a studies

#### Opera-1 (C201)

- 4-week antiviral activity, safety and PK data available
- TMC435 shows potent antiviral activity and is 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)

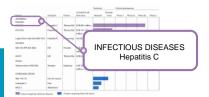
 PoC study in 37 patients with non-genotype-1 HCV infection – completed

## Phase 2b studies ongoing - includes approximately 950 patients

- PILLAR (C205) 386 genotype-1 infected treatment-naïve patients
- pragon (C215) 92 genotype-1 infected treatment-naïve patients
- ASPIRE (C206) 463 genotype-1 infected treatment-experienced patients







#### Late Breaker Oral Presentation for presentation at Monday 1 Nov. 17:45 (EST):

**LB-5**. "Efficacy and safety of TMC435 in combination with peginterferon α-2a and ribavirin in treatment-naïve genotype-1 HCV patients: 24-week interim results from the PILLAR study."

#### **Poster Presentations:**

- **278.** "In vitro studies investigating the mechanism of interaction between TMC435 and hepatic transporters." To be presented: Saturday 30 Oct, 14:00 (EST).
- **812.** "Virologic analysis of genotype-1-infected patients treated with once-daily TMC435 during the Optimal Protease inhibitor Enhancement of Response to Therapy (OPERA)-1 study." To be presented: Sunday 31 Oct, 08:00 (EST).
- **895.** "A Phase 2a, open-label study to assess the antiviral activity of TMC435 monotherapy in patients infected with HCV genotypes 2–6." To be presented: Sunday 31 Oct, 08:00 (EST).
- **1873.** "Pharmacokinetic-pharmacodynamic analyses of TMC435 in patients infected with Hepatitis C Virus (HCV) genotypes 2 to 6." To be presented: Tuesday 2 Nov, 07:00 (EST).



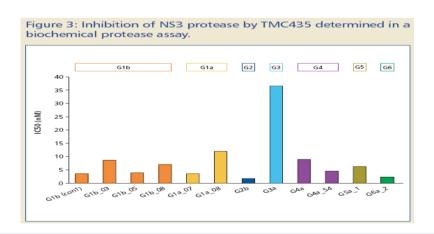
# TMC435 C202 phase 2a study with TMC435

### - as monotherapy in G2-6 infected patients

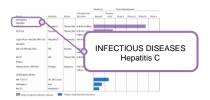
- Monotherapy with oral TMC435 200 mg QD for seven days resulted in potent antiviral activity in patients infected with HCV GT 2, 4, 5, and 6
- At Day 3 of TMC435 monotherapy, the mean (range) change from baseline in plasma HCV RNA (log10 IU/mL) was greatest for GT 6 (-3.57) and GT 4 (-3.43) cohorts, followed by GT 5 (-2.71) and GT 2 (-2.02) cohorts

### In vitro inhibition values of genotype 1 to 6 NS3/4A protease

 In vitro, TMC435 is a potent inhibitor of NS3/4A protease from genotype 1 to 6, with IC50 values below 13 nM for all except genotype 3A, with an IC50 value of 37 nM







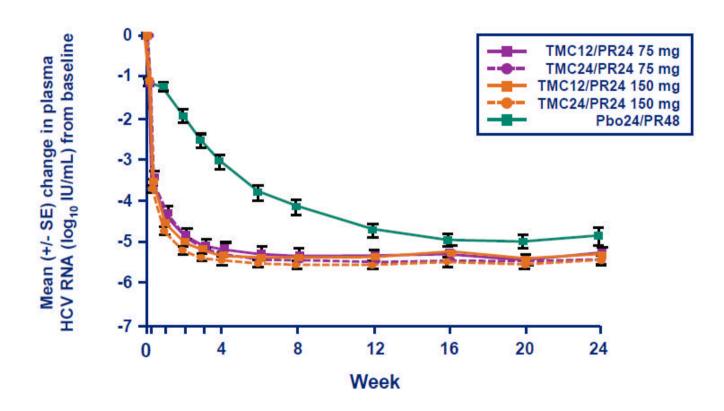
# TMC435 PILLAR Phase 2b study:

### 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</li>
- Both the viral breakthrough rate (4.9%) and relapse rate (1.6%) were low in the TMC435 treatment groups.



# PILLAR Week 24 Analysis: Mean Change in Plasma HCV RNA From Baseline

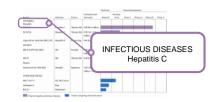


TMC435 treatment arms had a rapid and steep decline in HCV RNA during the first 4 weeks that was maintained throughout the 12- or 24-week triple-therapy dosing periods



### **TMC435 PILLAR**

## Virologic Response Overview



HCV RNA (<25IU/mL undetectable)	TMC12- PR24 75mg (n=78)	TMC24- PR24 75mg (n=75)	TMC12- PR24 150mg (n=77)	TMC24- PR24 150mg (n=79)	Pbo24- PR48 (n=77)			
Week 4 (RVR)	77% 59/77	68% 51/75	76% 58/76	79% 59/75	5% 4/75			
Week 12 (cEVR)	91% 71/78	96% 70/73	94% 72/77	97% 75/77	58% 43/74			
Week 24	94% 72/77	97% 70/72	94% 65/69	95% 69/73	82% 60/73			
Follow-up after planned end of treatment								
SVR4	91% 59/65	93% 56/60	93% 57/61	91% 62/68	n/a			
SVR12	97% 32/33	93% 27/29	89% 32/36	88% 28/32	n/a			

Potent and consistent antiviral effects demonstrated at Week 24 end-of-treatment



### PILLAR: Demographics and Baseline Disease Characteristics

Parameter	TMC12/ PR24 75 mg N=78	TMC24/ PR24 75 mg N=75	TMC12/ PR24 150 mg N=77	TMC24/ PR24 150 mg N=79	Pbo24/ PR48 N=77	All subjects N=386	
Patient demographics							
Male, %	51.3	62.7	55.8	55.7	50.6	55.2	
White, %	89.7	94.7	96.1	92.4	96.1	93.8	
Age, years, median	47.0	46.0	47.0	47.0	45.0	46.5	
Body mass index, median	25.9	24.2	24.7	24.9	25.6	25.0	
Disease characteristics							
HCV subtype 1a, %*	46.8	45.9	48.0	48.1	38.2	45.4	
HCV subtype 1b, %*	53.2	54.1	52.0	51.9	61.8	54.6	
HCV RNA, log <sub>10</sub> ≥800,000 lU/mL at baseline, median, %	82.1	84.0	89.6	91.1	81.8	85.8	
Metavir score F3, % <sup>†</sup>	12.8	22.7	9.1	15.2	9.1	13.7	
IL28B at baseline, CC, % <sup>‡</sup>	22.4	35.3	40.0	25.0	26.1	29.8	

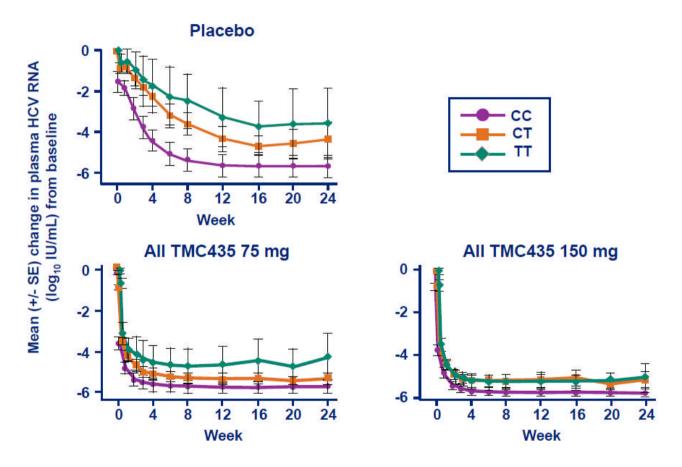
<sup>\*</sup>As determined by NS5B sequence-based assay



<sup>†</sup> Patients with cirrhosis (F4) were not eligible

<sup>&</sup>lt;sup>‡</sup> Polymorphism on chromosome 19 s12979860, data available for patients who consented only (67.9%)

# PILLAR Week 24 Analysis: Mean Change in HCV RNA from Baseline According to *IL28B* Genotype\*



In the TMC435 150 mg arms the CT or TT genotypes had rapid and steep decreases in HCV RNA, quite similar, although not identical, to the CC genotype.



### **PILLAR Week 24 Analysis: Adverse Events**

Preferred term, %	TMC12/ PR24 75 mg N=78	TMC24/ PR24 75 mg N=75	TMC12/ PR24 150 mg N=77	TMC24/ PR24 150 mg N=79	All TMC435 N=309	Pbo24/ PR48 N=77		
Adverse events leading to permanent discontinuation								
Discontinuation	9.0	2.7	9.1	7.6	7.1	7.8		
Most common adverse events*								
Headache Fatigue Influenza-like illness Pruritus Nausea	52.6 30.8 26.9 32.1 33.3	45.3 46.7 42.7 22.7 20.0	45.5 41.6 23.4 39.0 26.0	40.5 48.1 34.2 30.4 30.4	46.0 41.7 31.7 31.1 27.5	50.6 46.8 37.7 44.2 27.3		
Adverse events of interest								
Rash (any type) <sup>†</sup> Anemia <sup>‡</sup>	35.9 17.9	17.3 20.0	29.9 22.1	30.4 17.7	28.5 19.4	27.3 20.8		

<sup>\*</sup>Reported in ≥25% of subjects in the 'All TMC435' group (all dose groups combined)

TMC435 was well tolerated at all doses and regimens studied.



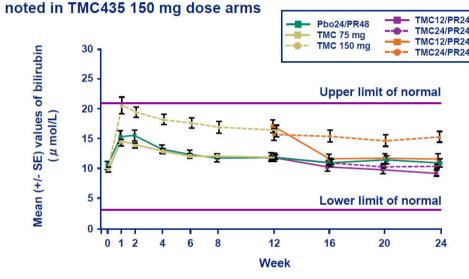
<sup>†</sup>Rash (any type) combines all reported types of rash

<sup>&</sup>lt;sup>‡</sup>Reported as an adverse event by study investigator if laboratory abnormalities considered clinically relevant

### TMC435 PILLAR

- laboratory parameters, bilirubin over time





- •Mild, non-progressive reversible elevations in bilirubin were noted in predominantly the TMC435 150 mg dose arms
- •Significant decreases in transaminases (ALT and AST) observed in all treatment groups.

The *in vitro* mechanism for the interaction between TMC435 and hepatic transporters has been investigated

TMC435 has affinity for the hepatic efflux and influx bilirubin transporters



### TMC435 PILLAR

### - Safety and Tolerability

- TMC435 was well tolerated at all doses and regimens studied.
  - No relevant differences in adverse events (AEs) between placebo and TMC435 treatment groups. 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.
  - 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.
- Significant decreases in transaminases (ALT and AST) were observed in all treatment groups.



## **PILLAR Week 24 Analysis**

### -Efficacy Summary

# TMC435 dosed once-daily with PegIFN/RBV over 12 or 24 weeks demonstrated potent antiviral activity

- At Weeks 4 and 12, HCV RNA was <25 IU/mL (undetectable) for the majority of patients in TMC435 groups
- The majority of patients in TMC435 groups (83%) met the criteria to stop treatment at Week 24
- •In patients who completed therapy at or before Week 24, response rates remained high (92%) 12 weeks after planned end of therapy
  - Addition of TMC435 to PegIFN/RBV increased response rates in all IL28B genotypes



## **PILLAR Week 24 Analysis**

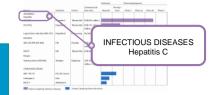
### -Safety Summary

# No clinically relevant difference in safety and tolerability between TMC435 and placebo groups

- Frequency of rash, gastrointestinal events, and anemia were similar to placebo group
- Mild and reversible increases in bilirubin concentration observed with 150 mg dose
- ALT concentration decreased in all treatment groups
- Discontinuation in TMC435 groups was low and similar to placebo group

Planning of Phase III studies of TMC435 is underway





### TMC435 - Recent events and upcoming 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 late Q4
- 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

