EUPATI Network Webinar

July 7th, 2016

Early collaboration – a recipe for solutions: drug development & treatment strategies may go hand in hand

The project is receiving support from the Innovative Medicines Initiative Joint Undertaking under grant agreement n° 115334, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies.

Early collaboration – a recipe for solutions: drug development & treatment strategies may go hand in hand

Welcome – please wait, webinar starting soon

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Welcome and introductions

Ingrid Klingmann
Chairman at European Forum for Good Clinical Practice (EFGCP)

Agenda

Time (CET)	What	Who
17.00	Welcome and introductions	Ingrid Klingmann, *EFGCP*
17.10	• "2 New Chemical Entities": problem description • Challenges implementing such a study • Multidrug resistance today	David Haerry, *EATG & EUPATI Consortium Member* Brian Woodfall, *Janssen, Pharmaceutical Companies of Johnson & Johnson*
17.40	Q & A	All
17.55	• "Nano suspension": Discovery and questions to advisors at early stage • Responding to scenario questions about a distant reality • Current development status nano suspension	David Haerry, *EATG & EUPATI Consortium Member* Brian Woodfall, *Janssen, Pharmaceutical Companies of Johnson & Johnson*
18.15	Q & A	All
18.30	Close of the Webinar	

HIV drug development – a success story but a bumpy road

- 1981: AIDS first reported
- 1984: AIDS identified as being caused by a human retrovirus
- 1987: AZT approval, first effective antiretroviral, but ineffective after some months – drug resistance not understood yet
- 1991, 1994: 2 additional NRTI approved; treatment with 2 substances understood as more effective
- 1995, 1996: breakthrough with 3 substances in PI class – 2 NRTI & 1 PI cocktail works long-term
- 1996 – 2003: Many patients lost life & hope due to accumulated multidrug resistance
- 2003: T-20 approved, treatment of last resort, injected twice daily, extremely expensive
- Multidrug resistance understood as biggest treatment hurdle to overcome

HIV drug resistance in SHCS

Patients with treatment initiation before 1999

- 56% have resistance mutations
- 18% with NNRTI resistance
- 54% NRTI resistance
- 28% PI resistance
- 22% 2-class resistance
- 11% 3-class resistance

Activists lobby for overcoming resistance

- Due to drug development history, many patients were exposed to single active drugs when entering pivotal trials
- Accumulation of multidrug resistance was the result
- Difficult treatment schemes, high pill burden and very demanding adherence requirements contributed
- Pivotal trial with two new compounds in two different drug classes understood to be a possible remedy – but where are the companies to run a joint pivotal trial?
- 2005: Tibotec understood resistance, 2 compounds in 2 classes in development almost simultaneously
- Lobbying FDA & EMA for accepting such a study successful

Patient engagement in defining relevance when designing a new treatment for a specific patient population

EUPATI WEBINAR

7 July 2016

Brian Woodfall; **Head of Development, Infectious Diseases and Vaccines**

DUET Phase 3 studies:

first time two investigational agents were studied in combination in a treatment-experienced patient study

Environment in early 2000s

- Concept Highly Active Antiretroviral Treatment (HAART) well established
- Multiple ARV classes and new agents emerging
- Increasing multi-drug resistance driven by prior inadequate therapy and successive functional monotherapy with new agents
- Large number of patients in developed world who had few or no treatment options with currently approved agents
  - Their hope for new active therapy relied on new investigational agents, which could only be accessed ‘one at a time’

Environment in early 2000s

- Patients and HCPs were pushing for access to multiple new investigational agents, active against drug resistant virus, to be used in combination
- Regulatory acceptance of such an approach, and at which stage of development, was uncertain
- Pharm companies were very reluctant to collaborate with their new investigational agents
  - Clinical trials, and most EAPs, prohibited concomitant treatment with other investigational agents

Tibotec situation 2005

- TMC114 (Darunavir) was an investigational PI designed to be active against drug resistant virus
  - Had shown substantial clinical benefit in the Phase 2b POWER studies
- TMC125 (Etravirine) was an investigational NNRTI with demonstrated activity against NNRTI resistant virus

Tibotec situation 2005

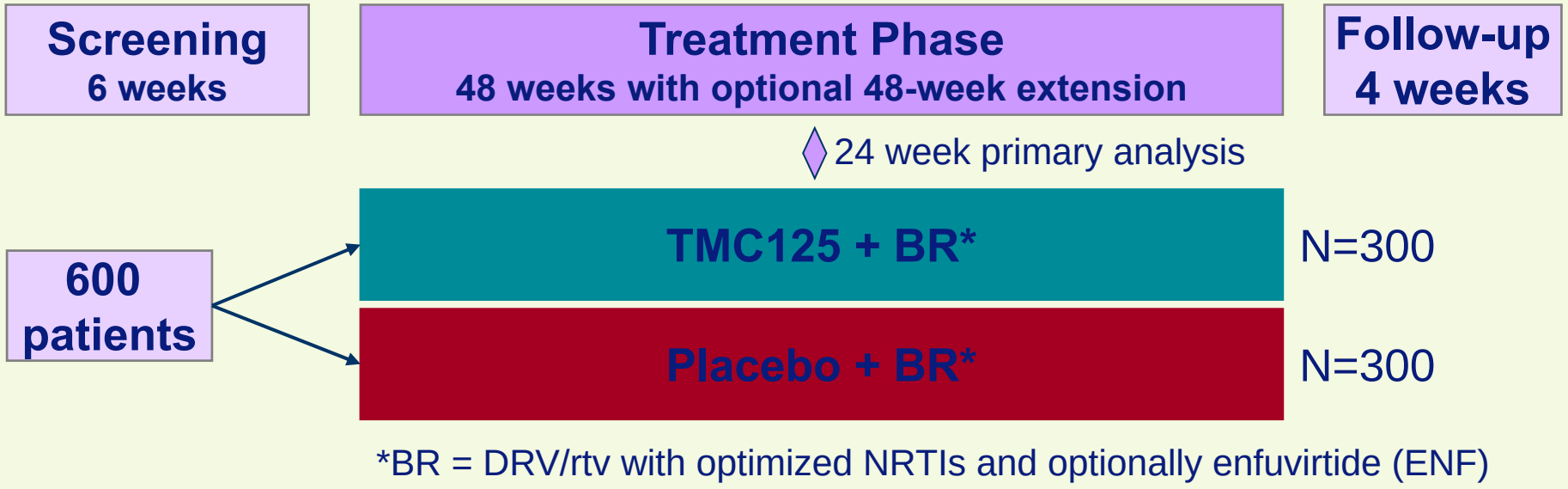
- Tibotec sought input from external stakeholders (HCPs, community advocates, and regulatory agencies) about the Phase 3 registrational trials for TMC125
  - Clear consensus was to address the patient population most in need of new active agents, those with multi-drug resistance
  - Very strong sentiment to allow the use of investigational TMC114 in the TMC125 Phase 3 trials

- Tibotec proposed plans, and sought consensus and approval, from internal stakeholders for such an innovative approach
  - Clinical, regulatory, drug safety, commercial, senior management, etc.

Risks for the company

- The activity of the background treatment may not allow for demonstration of benefit of TMC125
  - Risk of negative phase 3 study
- An unexpected / serious safety finding may be attributed to both investigational agents and affect both development programs
  - Potential to influence labelling (precautions or contraindications)/ monitoring/ clinical use
- Possible approval label to restrict the use of TMC125 only in combination with TMC114
  - Could deny some patients benefit from TMC125 if TMC114 could/would not be used
  - Commercial impact of such limitation

DUET Trials
Design and Major Inclusion Criteria



*BR = DRV/rtv with optimized NRTIs and optionally enfuvirtide (ENF)

- Plasma viral load at screening visit >5000 HIV-1 RNA copies/mL
- On a stable ART for at least 8 weeks at Screening, and willing to stay on that treatment until Baseline
- Documented genotypic evidence of resistance to currently available NNRTIs by having at least 1 NNRTI resistance-associated mutation present (either at Screening or on historical genotype)
- 3 or more primary PI mutations at Screening

DUET trials: Participating countries

DUET 1 (C206)

Argentina	66
Brazil	236
Chile	4
France	42
Mexico	14
Panama	6
Puerto Rico	3
Thailand	4
United States	237

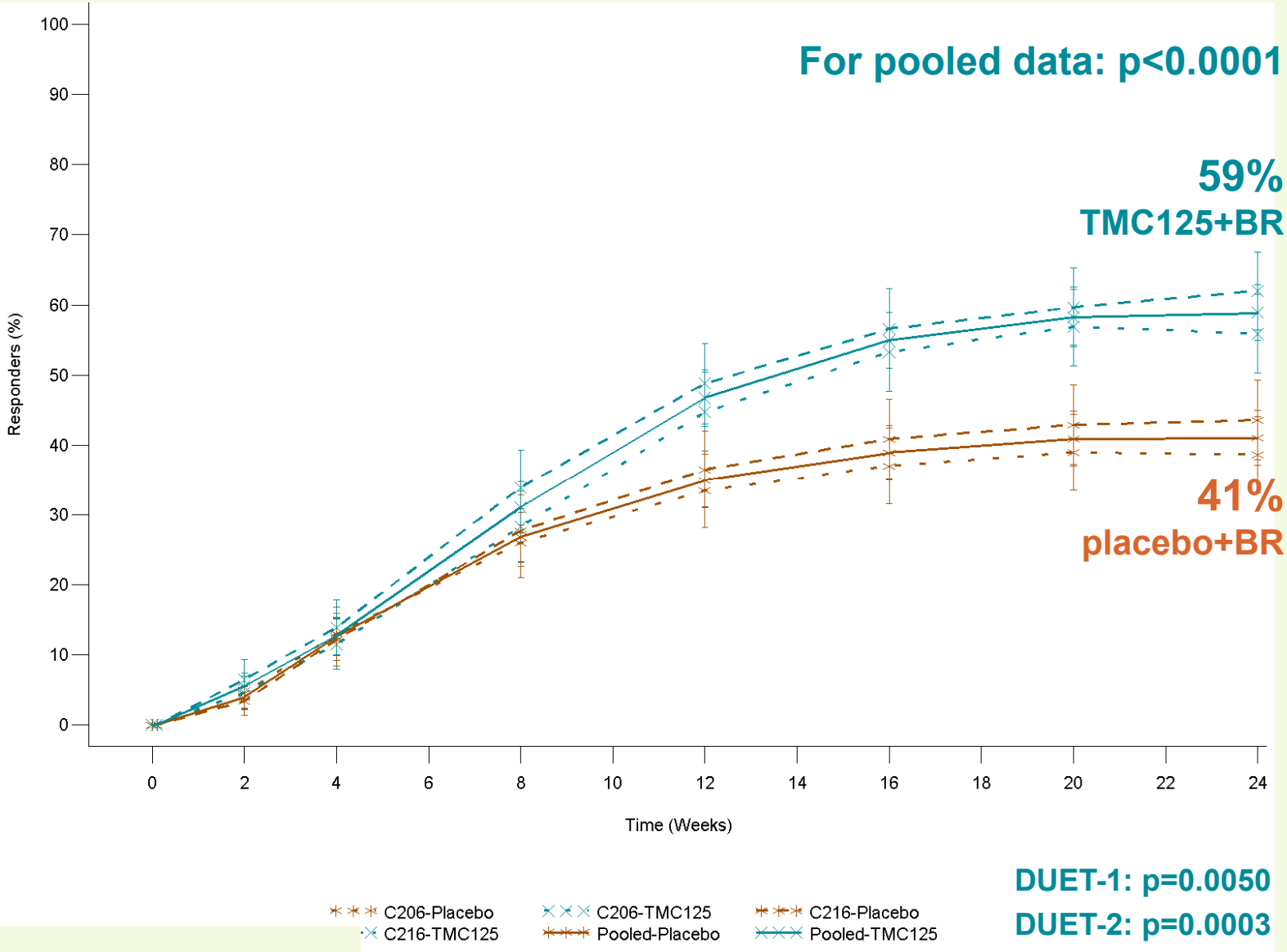
N=612

DUET 2 (C216)

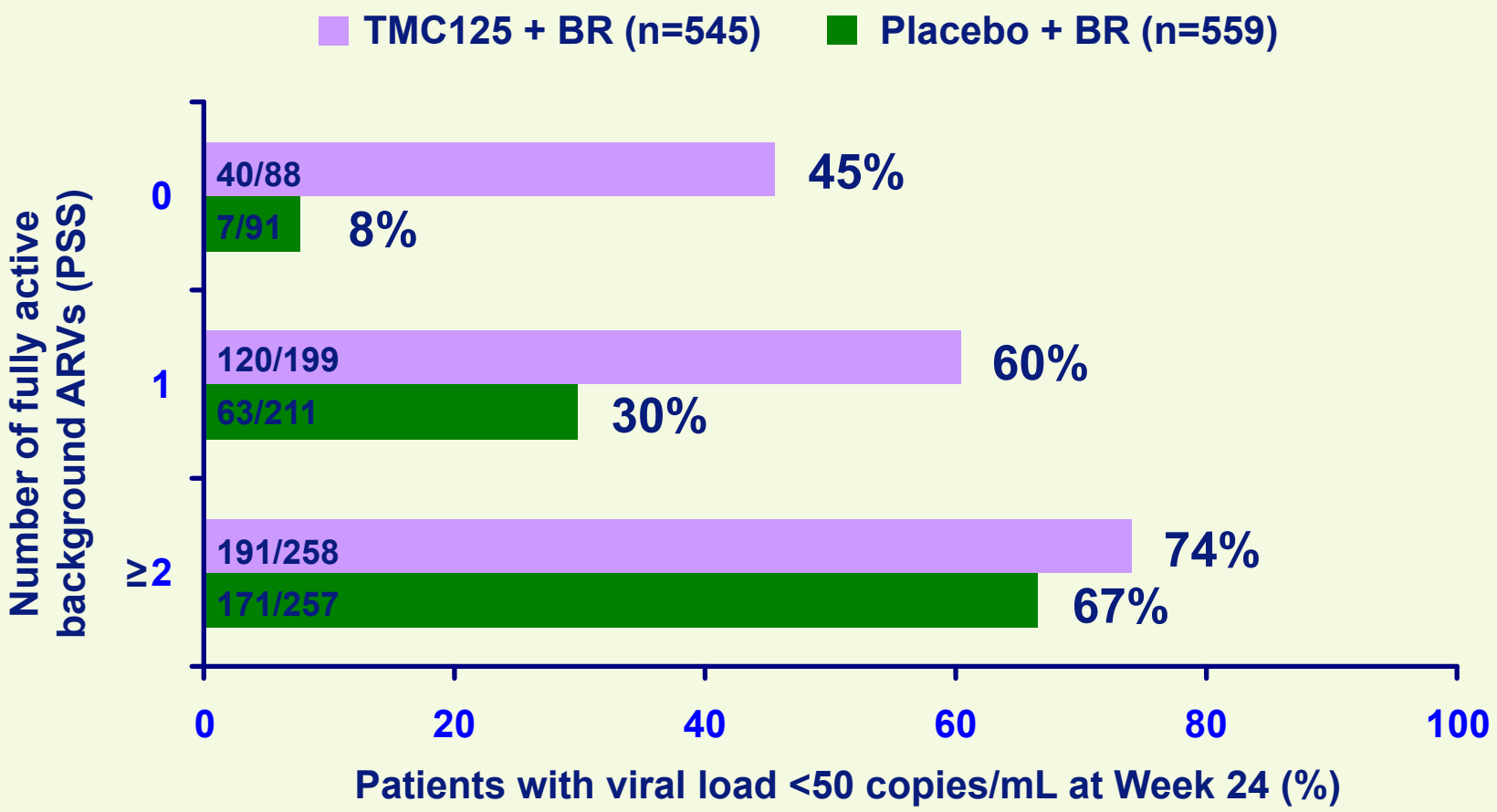
Australia	15
Belgium	14
Canada	42
France	102
Germany	61
Italy	70
The Netherlands	6
Poland	2
Portugal	1
Spain	23
United Kingdom	10
United States	245

N=591

Virologic Response Over Time (<50 copies/mL TLOVR)



Response (<50 copies/mL) according to number of active background ARVs



Analysis excludes patients who discontinued except for virological failure; PSS = phenotypic sensitivity score; darunavir and enfuvirtide are counted as fully active if FC<10 or used *de novo*, respectively

FDA Approved Label – Original Indication

- Etravirine is a HIV- 1 specific, non-nucleoside reverse transcriptase inhibitor (NNRTI) indicated:
  - In combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced adult patients, who have evidence of viral replication and HIV-1 strains resistant to an NNRTI and other antiretroviral agents.

EMA Summary of Product Characteristics

Section 4.1 Therapeutic indications

- Etravirine, in combination with a boosted protease inhibitor and other antiretroviral medicinal products, is indicated for the treatment of HIV-1 infection in antiretroviral treatment-experienced adult patients.

- The indication in adults is based on week 48 analyses from 2 Phase III trials in highly pre-treated patients where Etravirine was investigated in combination with an optimised background regimen (OBR) which included darunavir/ritonavir.

Patient engagement – lessons learned

- Involved patient advocates early and continuously through the design and execution of the Phase 3 program
- Included patient advocates and clinicians in the same advisory boards to maximize the interactions and value of the feedback
- Had patient representatives from US and EU review Phase 3 protocols prior to finalization
- Included patient representatives on the DSMB (Data and Safety Monitoring Board)
- Shared data in dedicated community group forums

Environment today

- The concept of individually optimizing HIV treatment regimens to maximize the number of new/fully active agents, including use of multiple investigational agents where appropriate, is now standard of care
  - the prevalence of drug resistance has declined substantially, particularly multi-drug resistance

- The approach of combining multiple investigational agents in specific infectious diseases has become quite common
  - Eg. Hepatitis C virus (HCV)

HIV drug resistance in SHCS

Patients with treatment initiation 2007-2013

- 10% have resistance mutations (1999: 56%)
- 4% with NNRTI resistance (18%)
- 5% NRTI resistance (54%)
- 2% PI resistance (8%)
- 1.7% 2-class resistance (22%)
- 0.2% 3-class resistance (11%)

Note: data applies to Switzerland and other Western European countries. Multidrug resistance continues to be a serious problem in resource limited settings (Africa, Eastern Europe). Side effect DUET trials: good collaboration between US & European activists

Q & A:

Please submit your questions using the Q &A function

Long Acting Rilpivirine (TMC278LA)

potential to improve adherence and convenience in HIV maintenance therapy

Environment in mid-2000s

- HIV treatments were evolving to more convenient less frequent dosing
  - Many once daily ARVs, moving toward fixed dose combinations (FDCs) and single tablet regimens (STRs)
- Poor adherence (both short and long term) emerging as major reason for treatment failure
- Janssen had specific expertise in long-acting injectable formulations in non-HIV disease areas
  - Could that technology be applied to ARVs?

Long-acting TMC278, a parenteral depot formulation delivering sustained NNRTI plasma concentrations in preclinical and clinical settings

G van't Klooster,[1] R Verloes,[1] L Baert,[1]
F van Velsen,[1] M-P Bouche,[2] K Spittaels,[1] J Leempoels,[3]
P Williams,[1] G Kraus,[1] P Wigerinck[1]

[1]Tibotec BVBA, Mechelen, Belgium; [2]Johnson & Johnson Pharmaceutical Research and Development, Beerse, Belgium; [3]Johnson & Johnson Pharmaceutical Research and Development, Merksem, Belgium

Formulation and preclinical methods

- Innovative nanosuspension*
  - 100mg TMC278 base per mL
  - particles of pure TMC278, average size of 200nm
  - sterile, stable formulation with neutral pH

- TMC278 LA single doses, given as intramuscular (IM) and subcutaneous (SC) injections to Sprague-Dawley rats and Beagle dogs
- PK and injection-site tolerability were evaluated

*using NanoCrystal® technology (under license from Elan Corporation, Ireland)
LA = long acting

Long-acting ARV formulations – A new paradigm?

- Uses of such formulations could include
  - once monthly injectable HAART
  - maintenance of undetectable viral load
  - prophylaxis
- Infrequent parenteral dosing offers potential advantages over daily (oral) treatment:
  - sustained concentrations of drugs in plasma
  - may improve adherence to therapy/prophylaxis
  - may avoid gastro-intestinal adverse events

Tibotec Advisory Board Meeting - The Concept of clinical development of antiretroviral agents for the maintenance of undetectable virus levels in people living with HIV infection.

Monday 10th December

Indication = Maintenance of undetectability in patients with undetectable viral load.
We envisage a regimen of intramuscular injection of TMC278 LA **and a second long-acting antiretroviral**, once a month or less often.

1.How large are the benefits of improving compliance in HIV infected individuals?

2. Will HIV infected individuals accept injections instead of a daily pill intake?

3. What regimen (dose volume and treatment duration) of injectable ARVs would be the best substitute for oral HAART, balancing convenient frequency of dosing with management of any side effects (both short and long-term)?

4. What would make a regimen of intramuscular injections of TMC278 LA and a second long-acting antiretroviral, once a month or less often, suitable for initial therapy in treatment-naïve patients?
In what circumstances can TMC278LA be used in an induction regimen rather than in a maintenance regimen?

5. What design of Proof-of-Concept study (3-6 months monitoring for breakthrough during a regimen of TMC278 LA + 2 oral NRTIs versus continued oral therapy?) would be most informative for the maintenance indication? After initial suppression with oral TMC278 + 2 NRTIs? After initial suppression with any standard of care first line therapy? What would increase acceptability of the design for IRBs/Ethics Committees and for Health Authorities?

6. In which populations would TMC278 LA + two oral nucleosides be preferred over current first line maintenance therapy (e.g. because of reduced pill burden)?
How large is the need to add TMC278 LA on top of current standards of care as an assurance of efficacy?

7. Where should we focus our search for a second or third long-acting ARV?

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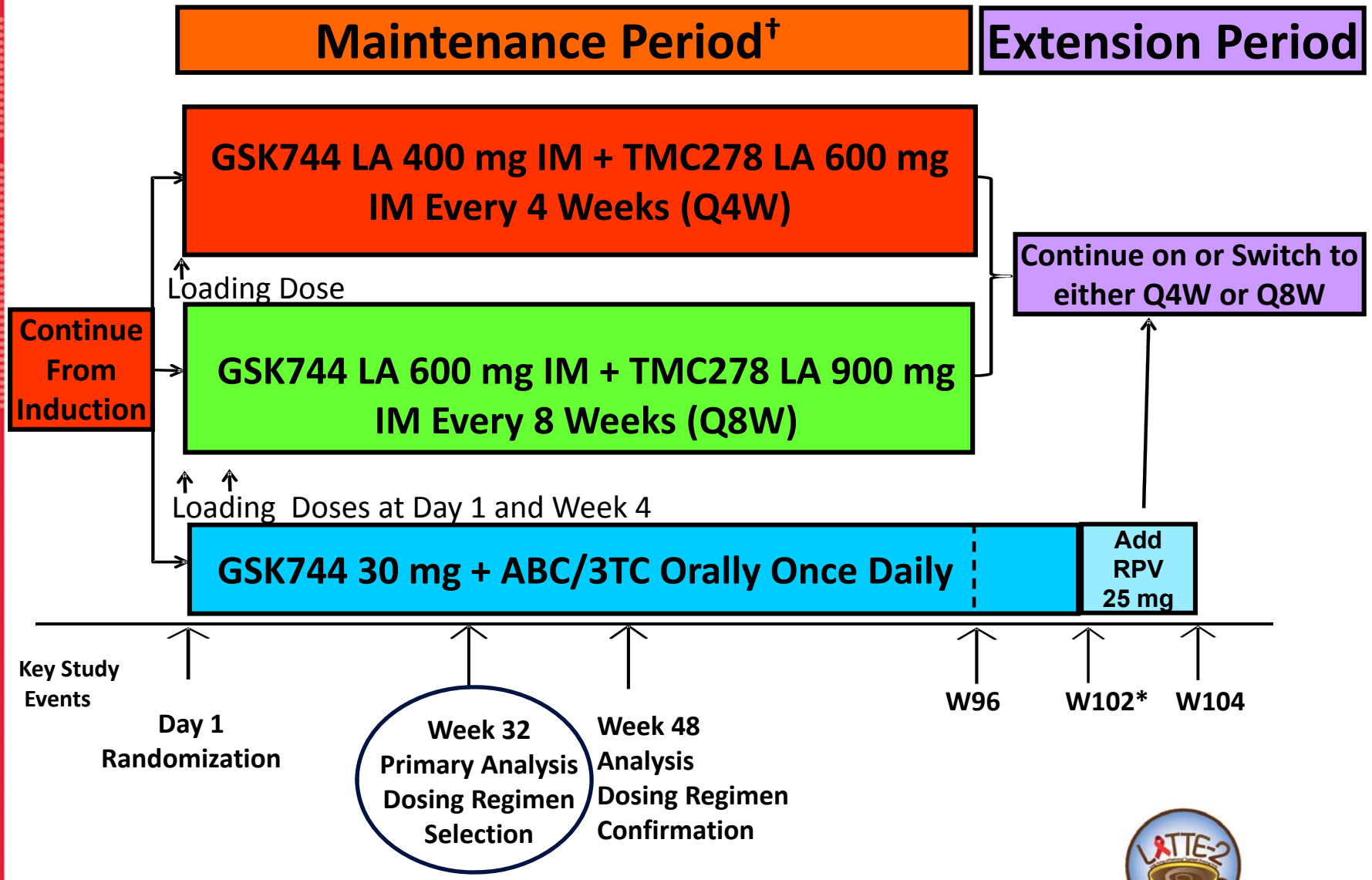
Advisory Board December 2007

Activist general concerns

- Resistance still big issue
- Long-term adherence challenging (achieving 95% life-long)
- GI side effects: minor for MD, major for patients quality of life
- ART could work as prevention, but how?

Despite lively & bad memories with injectable drugs, prospect of having a long-acting nano-suspension was exciting – if full regimen can be delivered by this route.
Use as prevention: very important especially if accessible in low income countries. Would address adherence issues effectively (adherence to prevention seen as even more challenging than treatment).
Concern: oral lead-in must be available

Study Design – Maintenance and Extension



†Subjects who WD after at least 1 IM dose enter Long Term Follow Up Period

*If eligible

ViiV – Janssen collaboration 2016

ViiV Healthcare to progress collaboration with Janssen to develop the first long-acting, two drug injectable regimen for treatment of HIV

London, UK, 7 January 2016 – ViiV Healthcare, a global specialist HIV company with GSK, Pfizer Inc. and Shionogi Limited as shareholders, today formalised its collaboration with Janssen Sciences Ireland UC (Janssen) for the phase III investigation and commercialisation of the long-acting, injectable formulations of cabotegravir (ViiV Healthcare) and rilpivirine (Janssen) for the treatment of HIV-1 infection. The long-acting formulations of cabotegravir (CAB LA) and rilpivirine (RPV LA) are being investigated as an injectable maintenance treatment for patients who have achieved viral suppression.

Long-acting injectables 2016

- LATTE2 32-week results presented in February 2016
  Conference report: http://www.aidsmap.com/Long-acting-injectable-cabotegravir-rilpivirine-works-well-as-HIV-maintenance-therapy/page/3038518/
- Other studies ongoing or planned (reviewing 2 phIII protocols now)
- Assumptions about strategic benefits made in 2007 still hold true
- Combination with integrase inhibitor class a happy coincidence
- Drug development is a long road…
- Looking forward to a long holiday without thinking about taking pills. A big relief especially when passing customs / borders of countries who don't want HIV-positive visitors (Emirates, Egypt, China, Iran and others)
- PrEP has become a successful prevention intervention for gay men in USA, France & other countries. Long-acting will make a difference.

Q & A:

Please submit your questions using the Q &A function

Thank you for attending