EU regulatory conditions for novel anti-infective drugs

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PK/PD relation

- In antimicrobial pharmacology the pharmacokinetic / pharmacodynamic relation relates some index of drug exposure (e.g., AUC, Cmin, time over a threshold concentration) to some measure of microbial drug susceptibility (e.g., EC50, MIC, multiples of these)

Focus on the PK/PD relation for an antimicrobial

- The emergence of therapeutic innovations and their implementation in clinical care, including drug development focused on pathogens selected as partially or fully resistant to previously approved agents, generate challenges for regulatory policy in the field of anti-infectives.
- European regulatory guidance to the industry for both antivirals and antibacterials have increasingly emphasized the exploration of the PK/PD relation, including activity against drug-resistant variants and the propensity for the selection of the same.
- Focus on the PK/PD relation and on the pathogen has impacted recommended trial endpoints, definition of trial populations, as well as the extent of the subsequent labeled indication.
- Examples follow from the fields of HIV, HCV, antibacterial and TB therapeutics

Example HIV therapy

Updated guidance for the development of antiretroviral agents

- In contrast with the approach taken in prior guidance, the 2013 revision defines trial populations according to documented viral resistance rather than treatment histories.
- In the update, the term *treatment naïve* refers to patients who have not previously received antiretroviral therapy, *and who are infected with HIV without mutations conferring drug resistance* in their major viral populations, as determined by standard genotypic assays (i.e. virus that is predicted to be fully susceptible to the test agent).
- The term *treatment experienced* is not used since it does not adequately define a patient population that is harboring drug-resistant viruses.
- Instead, the focus is on the evaluation of the in-vitro and in-vivo activity of a new agent against HIV, including virus with demonstrated resistance that is relevant to the class to which the new agent belongs.

Rationale for the change of focus

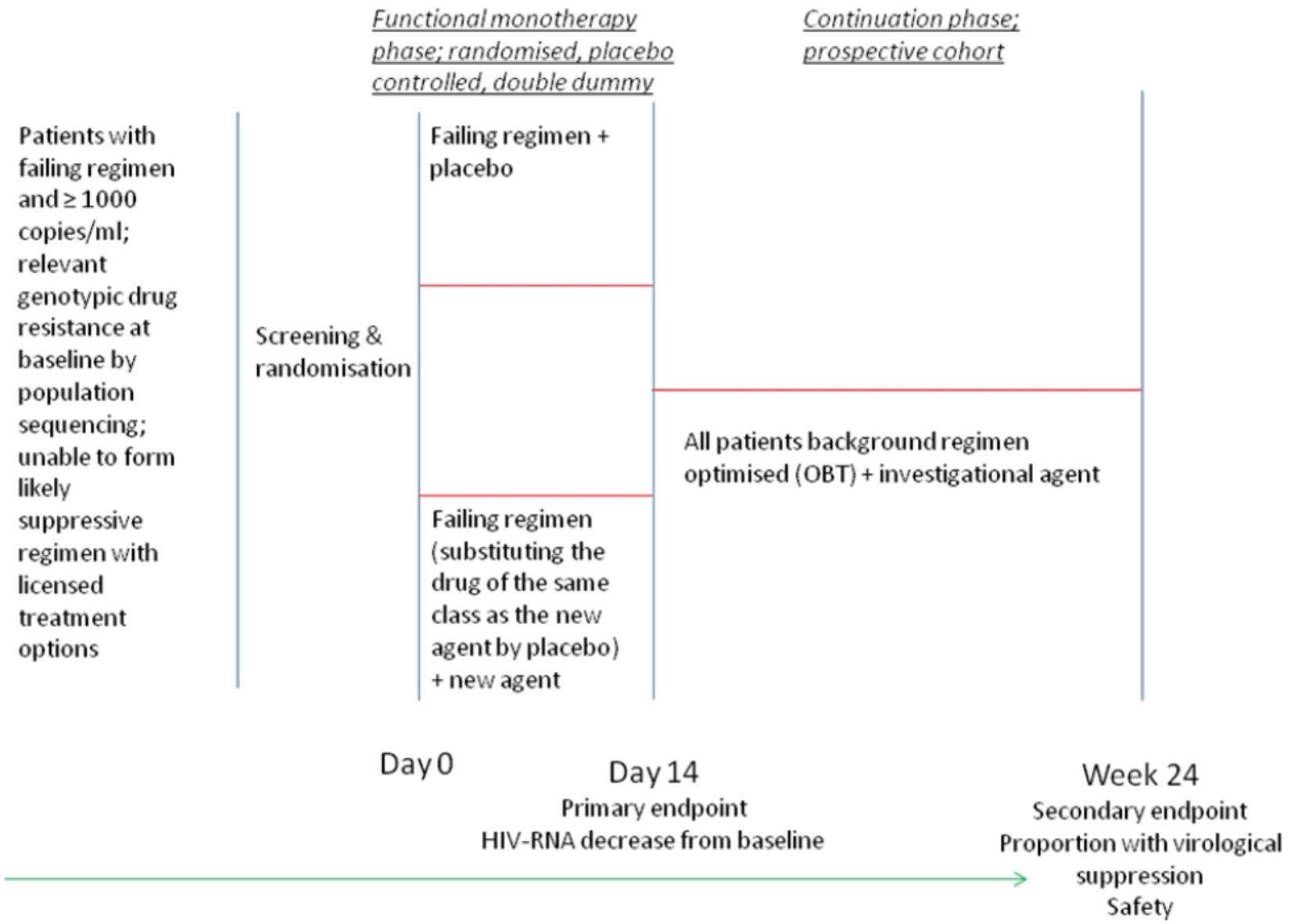
- Due to the introduction of more effective and tolerated treatment regimens, the development of extensive resistance *de novo* is now rare in patients who are treated with optimized regimens in the EU – the great majority of “treatment experienced” patients (that have experienced “virological failure”) have virus that will be fully susceptible to a *n*-th line regimen
- As a result, placebo- controlled superiority designs are no longer feasible and non-inferiority trials in such populations are fraught with methodological problems.

The elements of the proposed trial program

- For all new agents, it is proposed that data on safety and efficacy are generated in randomized double-blind controlled trials in *treatment naïve patients*.
- For first agents of a new class, and in the absence of any known cross resistance to the new class, such data might suffice for an indication encompassing all HIV-infected patients.

Studies is patients with resistance relevant to the class of the new antiretroviral

- Additional data would be required to support the use of new agents of existing classes in patients *infected with virus with resistance to other members of the class to which the new agent belongs*.
- In this setting data should be generated from one or more studies that include *a short initial randomised controlled period during which patients continue their failing regimen with or without addition of the new agent* followed by a longer period during which *all patients are treated with the new agent* in association with an optimised background regimen.



The format of the labeled indication (SmPc section 4.1.)

(Product name) is indicated, in combination with other antiretroviral medicinal products, for the treatment of adults infected with HIV-1 without present or past evidence of viral resistance to agents of the X class (see section 5.1.).

The X class is the class to which the new agent belongs.

If a study in patients with “class resistance” has also been performed with successful outcomes, a wider indication could be supported

(Product name) is indicated, in combination with other antiretroviral medicinal products, for the treatment of HIV-1 infected adults (see section 5.1.)

Example hepatitis C virus (HCV) therapy

HCV genotypes

- Based on phylogenetic relations, HCV is divided into 6 genotypes and numerous subgenotypes
- The genotypes are intrinsically *differently difficult to clear* (different activity of host innate immunity against different genotypes), spontaneously in acute infection, or with antiviral therapy
- GT1 most difficult to cure > GT 4, GT 3 > GT 2
- In US/ Europe GT 1 is predominant, followed by GT 2/3
- The patterns of activity (EC50 as well as barrier to resistance) of many but not all diract acting antivirals (DAA) are genotype- and subtype dependent, with some agents showing *in vitro* and clinical activity only against certain genotypes.

Selected aspects of the PK/PD characterisation of a direct acting antiviral against HCV

- A determination of the antiviral activity (EC50/90) in cell based HCV replicon assays representing the different HCV genotypes and subtypes.
- For each viral genotype/subtype, an assessment of the in-vitro selection of resistant variants and characterisation of their phenotypic and genotypic properties.
- Characterization of the activity of the new agent against viruses/replicons (which may include clinical isolates or site directed mutants) harbouring a range of resistance associated mutations.
- A characterisation of the in vivo dose/exposure relation in patients
- An investigation of its antiviral effect in short term monotherapy
- A characterisation of its clinical efficacy against common pre-existing viral variants as well as its resistance pathways in vivo

The correlation of activity against the HCV replicon and in vivo monotherapy – example simeprevir

Genotype	EC50 *fold-change* of clinical isolates (con1 reference, 9.4 nM)	Plasma HCV-RNA decline after 7 days of monotherapy
1	0.4-1.4	-4.18
2	11	-2.73
3	1014	-0.04
4	0.3	-3.52

Example: the extrapolation of the efficacy of sofosbuvir+simeprevir from genotype 1 to genotype 4

- Genotype 4 is not intrinsically more difficult to treat than genotype 1
- SOF shows similar EC50 in both genotypes; no naturally occuring polymorphisms to reduce activity in either genotypes; similar resistance selection in vitro (truly pangenotypic activity)
- SMV shows similar EC50 in both genotypes; naturally occuring polymorphisms impacting response are more common in GT1a; similar resistance pathways in vitro and in vivo; similar activity on short term monotherapy
- The clinical efficacy of SOF+RBV or SOF+PEG+RBV is not lower in GT4 compared to GT1
- The clinical efficacy of SMV+PEG+RBV is not lower in GT4 compared to GT1
- As *combination effects* of antivirals are not anticipated to be genotype specific, SOF+SMV should be highly effective in GT4

The indication for Incivo (telaprevir), 2011

INCIVO, *in combination with peginterferon alfa and ribavirin*, is indicated for the treatment of *genotype 1* chronic hepatitis C in adult patients *with compensated liver disease* (including cirrhosis):

- who are *treatment-naïve*;

- who have *previously been treated* with interferon alfa (pegylated or non-pegylated) alone or in combination with ribavirin, including relapsers, partial responders and null responders (see sections 4.4 and 5.1).

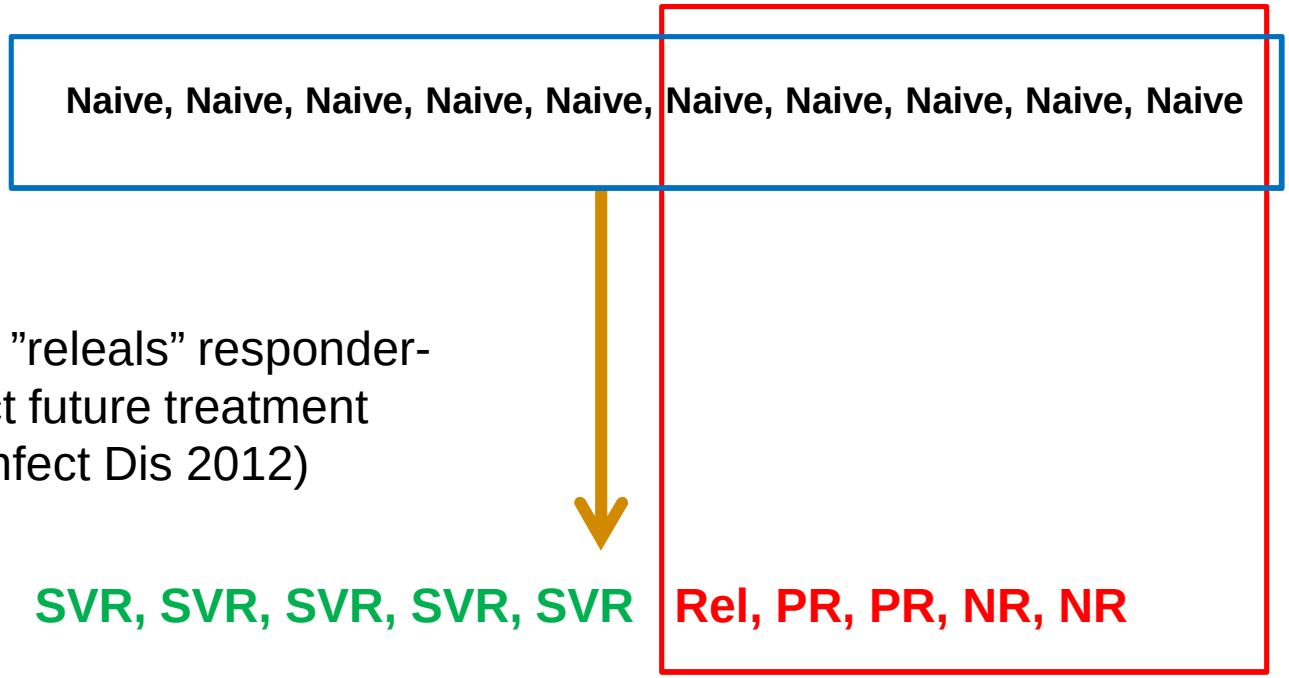
Reflections on the interferon-free treatment paradigm – analogies with HIV

- Combination therapy is anticipated in all cases
- Agents with different mechanisms of action or lack of cross-resistance consistently show additive antiviral effects
- Failure of antiviral therapy is in many cases associated with selection of drug-resistant viral variants which may impact future therapeutic option. Furthermore, in hepatitis C, there are naturally occurring viral polymorphisms that impact the activity of some agents.
- Consequently, individual viral drug susceptibility will need to be taken into account when selecting an appropriate combination regimen

Treatment naive ↔ treatment experienced

- Insofar as the term “treatment-experienced” refers to patients that have been treated with PEG+RBV but have not been treated with a DAA, this population is in no way analogous to a “treatment-experienced” human immunodeficiency virus (HIV) population.
- Whereas the virus of the latter have been subjected to selection pressure for antiviral resistance, and in many cases harbour virus with reduced susceptibility to one or more antivirals, PEG+RBV does not select for viral resistance (this being essentially an immune therapy).

Treatment experienced patients (PEG/RBV) form a ”functional subgroup” of a previously untreated population



Treatment with PEG/RBV ”releals” responder-status but does not impact future treatment response (Liu et al, Clin Infect Dis 2012)

Patients that do not achieve SVR tend to have more fibrosis, higher baseline HCV-RNA and be IL28 non C/C (negative prognostic baseline factors)

The revised indication for direct acting antivirals against HCV 2014-

"[TRADENAME] is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults (see sections 4.2, 4.4 and 5.1).

For hepatitis C virus (HCV) genotype specific activity, see sections 4.4 and 5.1."

- The recommended regimens to use in different situations is specified in section 4.2.
- Warnings and precautions (e.g., due to lack of efficacy against certain genotypes) are specified in section 4.4
- Efficacy data are given in section 5.1.

Example, agents for the treatment of multi-resistant bacteria

PK/PD according to guidance on antibacterials

- As opposed to HIV and HCV, animal models are anticipated to provide information for the PK/PD characterisation of antibacterials
- Whenever possible it is recommended that the PK/PD analyses used for dose regimen selection should be based on PK data obtained from infected patients rather than from healthy subjects.
- For some, but not all, test antibacterial agents the PK/PD relationship may be sufficiently straightforward and well-described that sponsors consider it possible to omit clinical dose-finding studies and to evaluate the efficacy of one or a very few regimens.
- The use of PK/PD to predict the optimal duration of treatment is not well established at present

Specific concerns for drug development against multi-resistant pathogens

- If the antibacterial spectrum and pharmacokinetics of the test agent permit, the preferred approach would be to obtain clinical data from *at least one randomised and active controlled study in a specific type of infection*.
- These studies are not expected to enrol sufficient numbers of patients infected with multi-resistant organisms to allow for an assessment of efficacy, although any cases that are enrolled should be carefully scrutinized for outcomes.

What is the underlying philosophy of this?

Principle of bridging a clinical efficacy demonstration to uncommon multiresistant pathogens

Pathogen	Pathogen drug susceptibility A	B	C	D	E	F	G	H	I
Test agent	s	s	s	s	s	s	s	s	s
Reference agent	r	r	r	r	s	s	s	s	s

In vitro – in vivo bridge

Pathogens resistant to approved agents

Spectrum of microbes for which non-inferiority is shown

Still, some clinical efficacy data against the target pathogen is preferable

- It is highly desirable that some pre-approval evidence is provided to support a claim for clinical efficacy against target multi-resistant pathogens, even if is based only on well-documented cases collected from a prospective non-randomised study that enrols patients regardless of the site of the infection

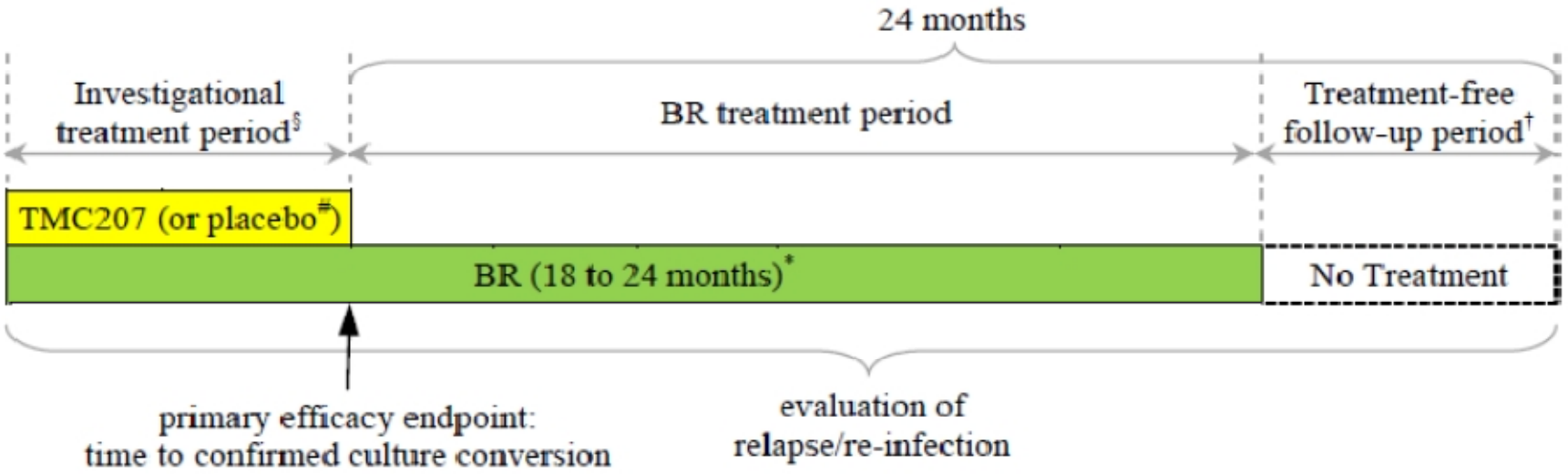
Subsequent labeling considerations

- Provided that non-inferiority is convincingly demonstrated for the test product compared to the active comparator *in a specific clinical syndrome*, the evidence accumulated could then be used to support a claim for efficacy against specific multi-resistant organisms in this indication, assuming that the safety data collected would also support a conclusion of a favourable B/R relationship.
- In addition, depending on non-clinical data and detailed knowledge of the PK of the test agent, consideration could be given to allowing an indication for use in patients infected with specific multi-resistant organisms when causing other types of infection under specified circumstances. *Thus, a pathogen-specific indication is a possibility*.

Example agents for the treatment of TB

The pivotal study for bedaquiline

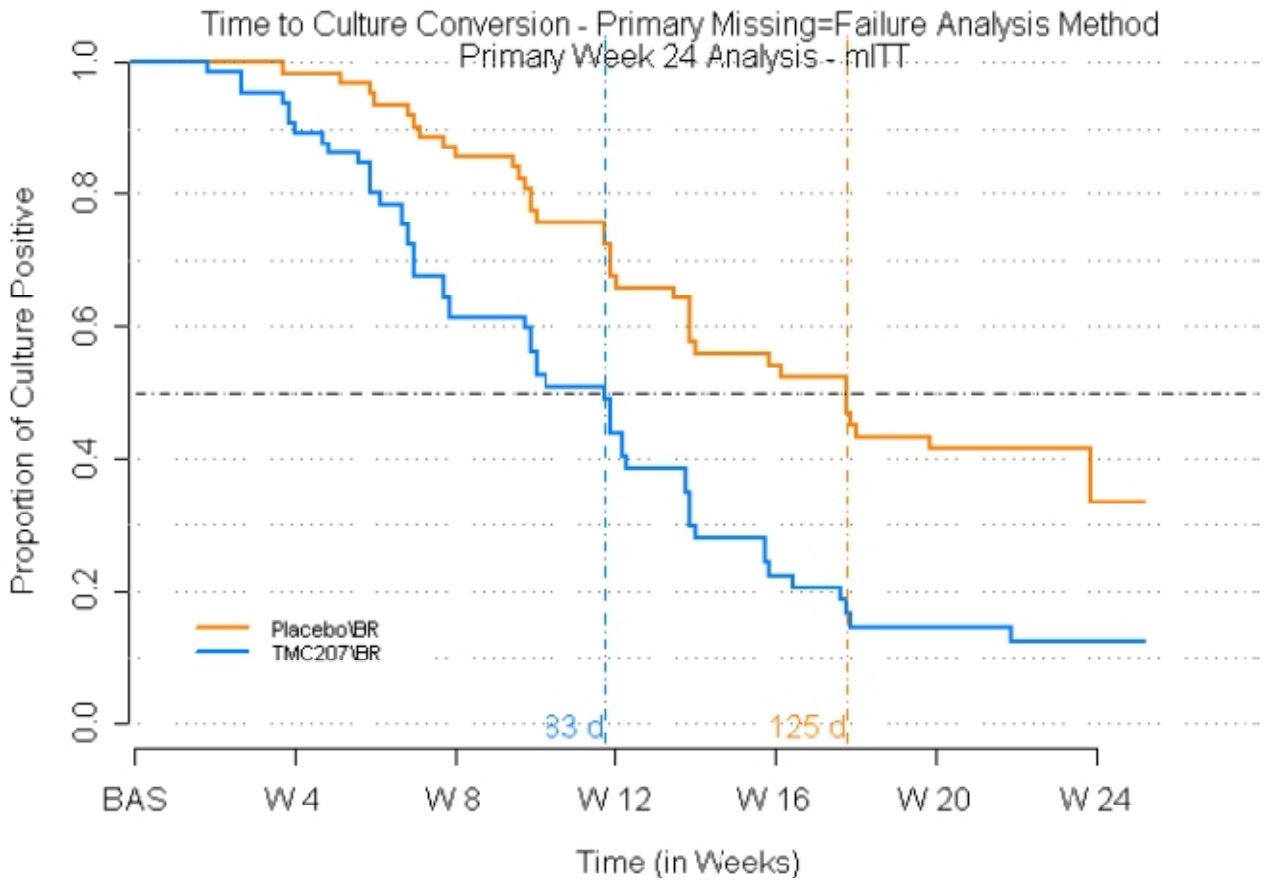
- Approval based on phase II placebo-controlled, double-blind, randomised trial in subjects with sputum smear-positive pulmonary infection with multi-drug resistant (MDR or pre-XDR) *Mycobacterium tuberculosis*.
- BDQ compared to placebo as add-on for 24 weeks (pivotal stage II of study) to a preferred background regimen consisting of the 5 agents was given for 18-24 months (at least 12 months after the first documented negative culture): KAN, OFL, ETH, PZA and cycloserine/terizidone.



§ 8 weeks in C208 Stage 1 and 24 weeks in C208 Stage 2 and C209.

Primary endpoint – time to sputum culture conversion. This was shorter in the bedaquiline group compared to the placebo group; median time to culture conversion 83 vs 125 days, ($p < 0.0001$)

Figure 6: Proportion of Culture Positive Subjects Over Time – mITT



The primary endpoint was supported by indications that the additive effect of BDQ was greater the lower the activity of the baseline regimen

Table 17: Culture Conversion Rates at Week 24 by BR activity (C208 Stage 2, C209) – mITT

No of active agents in baseline BR	C208 Stage 2				C209	
	bedaquiline/BR		Placebo/BR		bedaquiline/BR	
	N	24 week responder (missing = failure) n (%)	N	24 week responder (missing = failure) n (%)	N	24 week responder (missing = failure) n (%)
0	-	-	-	-	14	9 (64)
1	-	-	3	2 (67)	28	18 (64)
2	13	8 (61)	8	3 (37)	36	27 (75)
3	20	17 (85)	22	14 (64)	58	51 (88)
4	17	15 (88)	13	4 (31)	21	17 (81)
5	4	3 (75)	10	8 (80)	8	7 (87)
Resistance of TB strain						
MDR HR	39	32 (82)	45	28 (62)		
Pre XDR	15	11 (73)	12	4 (33)		
PZA res	38	28 (74)	33	16 (48)		
PZA susc	18	16 (89)	25	16 (64)		

The addition of BDQ to the regimen protected against emerging resistance to the other drugs

Table 27: Emergence of Resistance to Anti-TB Drugs in study C208 stage 2– final analysis mITT

	Agar proportion			
	bedaquiline/BR		Placebo/BR	
Drug	N	n	N	n
Any compound	12	2	31	16
Ofloxacin	10	0	27	7
Kanamycin	7	0	25	1
Capreomycin	8	1	25	1
Pyrazinamide	2	0	11	2
Ethionamide	11	0	28	2
Ethambutol	4	1	15	6
Streptomycin	2	1	5	1
PAS-C	10	0	29	1
INH (high dose)	-	-	1	1

N = number of subjects' isolates having paired data and whose isolate was susceptible at baseline for the considered drug; n – number of subjects' isolates with emerging resistance for the given drug;

Conditional approval of bedaquiline

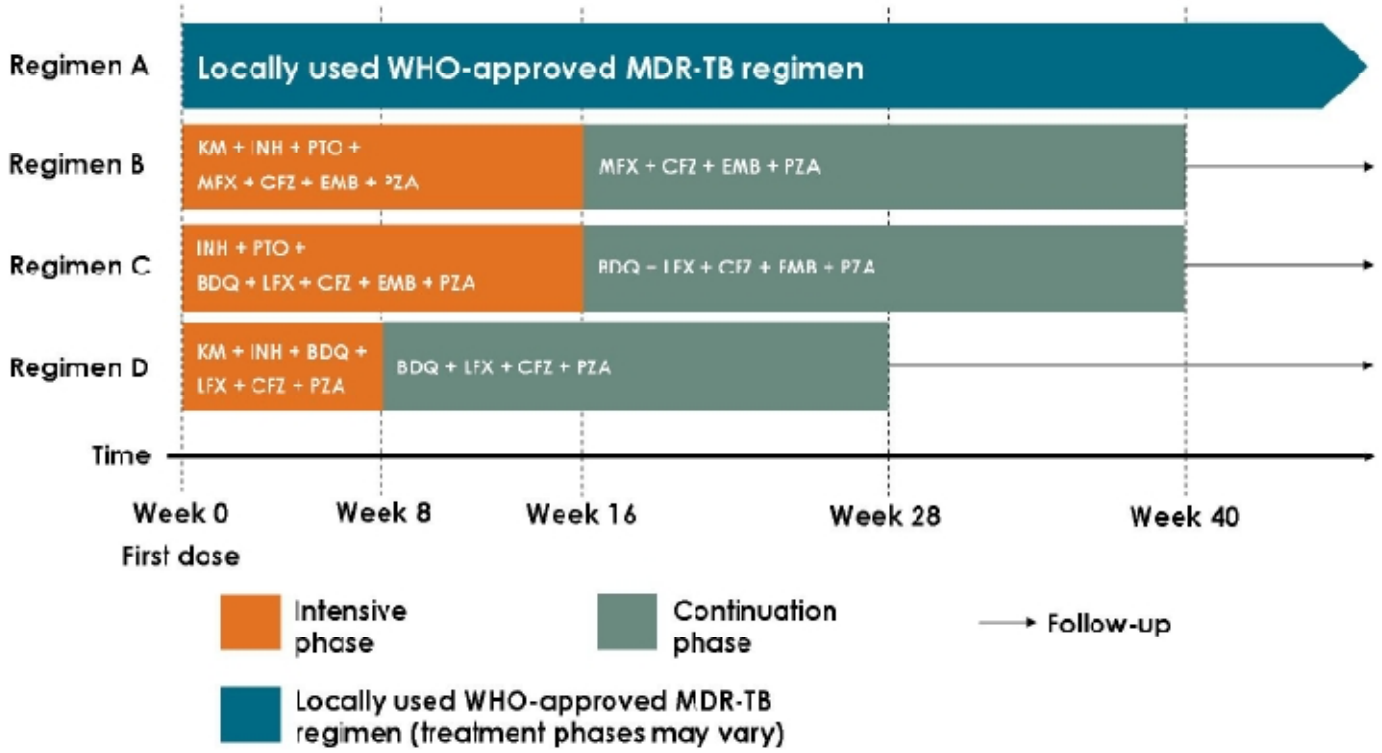
- SIRTURO is indicated for use as part of an appropriate combination regimen for pulmonary multidrug resistant tuberculosis (MDR TB) in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability. See sections 4.2, 4.4 and 5.1.
- Main condition – the investigation of the efficacy and safety of bedaquiline in the STREAM study

Note: The surrogacy of time to sputum conversion was recently corroborated by the ReMoxTB study

The design of the confirmatory STREAM study

The first primary objective in Stage 2 is to assess the superiority of Regimen C over Regimen B; this is a US FDA requirement. The other primary objectives of Stage 2, of particular relevance to treatment programs, are to assess whether Regimen C is not inferior to Regimen B and to assess whether Regimen D is non-inferior to Regimen B. (NIM -10%)

Figure 8: Treatment phases of investigational regimens



Conclusion

An appropriate consideration of the PK/PD relation allows for the utilisation of data from all parts of the drug development program (e.g., in vitro antimicrobial activity, animal models, resistance analysis) to bridge available clinical efficacy data from well-studied populations to populations and scenarios where results from a full clinical study program are not available

This provides the possibility to:

- slimline clinical drug development (potentially cost-saving)
- confidently infer B/R also for less common pathogens that may not be amenable to study in a full clinical program
- more rapidly bring crucial drugs to the full population anticipated to benefit