HIV FORUM MEETING
10-11 January 2008

CHALLENGES
IN DESIGNING CLINICAL TRIALS
IN HEAVILY PRETREATED PATIENTS

Nathalie Morgensztejn, responsible for the clinical assessment
in Infectiology, Afssaps, France
and EMEA representative for the HIV Forum

Main challenge

- To assess the benefit/risk of a drug without compromising the patient's virologic response to subsequent lines of ARV therapy

- Up to now : OBT + Test versus OBT (enfuvirtide, darunavir, maraviroc, raltegravir)
  - Risk for patients : only being exposed to recycling drugs or being exposed to a functional monotherapy *(latter situation being considered as more deleterious as regards risk of resistance)*

GSS/PSS <2 : around 40- 50% of the population enrolled in clinical studies in salvage therapy

HIV-drug	Clinical trial	PSS = 0		PSS = 1	
		Test	Control	Test	Control
Raltegravir	BENCHMRK-1	44/232 **(19.0%)**	21/118 **(17.8%)**	67/232 **(28.9%)**	39/118 **(33.1%)**
	BENCHMRK-2	23/230 **(10.0%)**	23/119 **(19.3%)**	78/230 **(33.9%)**	32/119 **(26.9%)**
Darunavir/r	POWER-1	15/55 **(27.3%)**	8/52 **(15.4%)**	17/55 **(30.9%)**	22/52 **(42.3%)**
	POWER-2	13/64 **(20.3%)**	9/61 **(14.8%)**	21/64 **(32.8%)**	16/61 **(26.2%)**

HIV-drug	Clinical trial	GSS = 0		GSS = 1	
		Test	Control	Test	Control
Raltegravir	BENCHMRK-1	70/232 **(30.2%)**	34/118 **(28.8%)**	76/232 **(32.8%)**	48/118 **(40.7%)**
	BENCHMRK-2	45/230 **(19.6%)**	31/119 **(26.1%)**	102/230 **(44.3%)**	48/119 **(40.3%)**
Maraviroc	MOTIVATE-1	59/235 **(25.1%)**	31/118 **(26.3%)**	80/235 **(34.0%)**	29/118 **(24.6%)**
	MOTIVATE-2	43/191 **(22.5%)**	20/91 **(22.0%)**	58/191 **(30.4%)**	24/91 **(26.4%)**
Tipranavir/r	RESIST-1	43/311 **(13.8%)**	53/309 **(17.2%)**	113/311 **(36.6%)**	117/309 **(37.9%)**
	RESIST-2	19/271 **(7.0%)**	24/268 **(9.0%)**	76/271 **(28.0%)**	69/268 **(25.7%)**

Disputable design OBT +A vs OBT for patients with GSS< 2

- GSS = 0
  - Control arm : only recycling drugs
  - Test arm : functional monotherapy with A
- GSS = 1
  - Control arm : functional monotherapy with the active drug in OBT
  - Test arm : acceptable

Are regulatory requirement and clinical practice compatible ?

- For GSS = 0
- For GSS = 1

For GSS = 0

- Risk of functional monotherapy UNLESS 2 drugs in development can be proposed
- HOWEVER, if patients enrolled in OBT + A + B :
  - Non comparative AND 2 drugs in development => *No reliable efficacy/safety data can be derived=>does not meet regulatory requirement*

FOR GSS = 1

- 1 drug in development : dilemma for the comparator arm (functional monotherapy)

- Need for 2 drugs in development to avoid functional monotherapy in both treated and comparator arm
  - *2drugs at the same stage of development was rare up to now (also problem of co-sponsoring)*
  - *True effect of individual drug might be difficult to appreciate*

How to solve the dilemma of assessing drugs but avoiding functional monotherapy?

- Open label non comparative study in patients with GSS<2 with historical comparison (Lederman, AIDS 2007) ?

- « Cross-over » designs (de Gruttola, AIDS Res and Hum Retrov 2007)

1. Open label non comparative study in patients with GSS<2 with historical comparison?

- Would amount considering that the response to treatment could be predicted with sufficient confidence rendering randomisation no longer compulsory, *which remains to be demonstrated*

- Reference is made to clinical development programme in cancer : but randomised comparative studies is the general rule (CHMP/EWP/205/95)

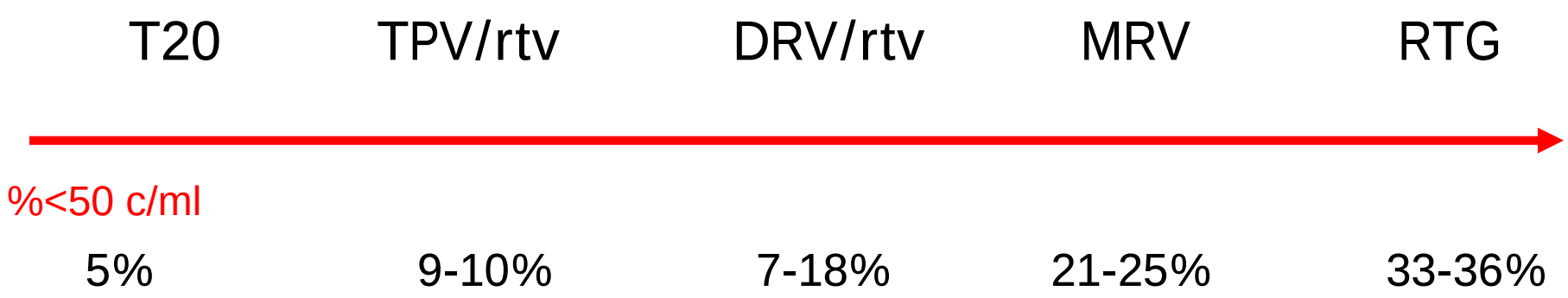
Can historical comparison be the *unique* basis for approval?

- Difficulties as regards the benefit assessment
- Difficulties as regards the risk assessment
  (Questionable ability of non comparative trials to raise safety signals)

=> Difficulties as regards the benefit/risk assessment

Difficulties in interpreting historical data in the benefit assessment (1/2)

- Response rate in OBT is evolving (depending on the availability of new therapeutic options)
  - As illustrated by :



Difficulties in interpreting historical data as regards the benefit assessment (2/2)

- Use of T20 is also evolving (potential statistical interaction)
  - As illustrated by :

	TPV/rtv	DRV/rtv	MRV	RTG
Test	15%/38%	45%/54%	10%/20%	38%/38%
Control	9%/34%	43%/55%	11%/18%	36%/39%

Difficulties in the risk assessment (1/2)

- Could we have detected higher rate of CXR4 shift associated with virological failure with CCR5 inhibitors as compared to the natural shift ?

Tropism at failure	R5	X4 OR R5/X4	Non typable
Maraviroc Treated = 836 Failure = 113	31%	56%	13%
Placebo Treated n=209 Failure n=89	90%	4%	6%

Difficulties in the risk assessment (2/2)

- Could we have detected a signal towards an increase risk of tumours with raltegravir?
  - Rate of tumours as expected in the published literature
  - However, higher number than in the comparator arm, justifying a specific risk management programme

2. « Cross over » design

- OBT + A vs OBT with early switch to A for the control arm
  - Need for early switch to reduce the time of functional monotherapy in the comparator arm
    - Study period before switch might be too short for adequate comparative efficacy/safety assessment
    - After switch medium/long term data are no longer comparative as regards efficacy/safety (=>observational study)

EMEA Guidelines on anti-HIV drugs
(EMEA/CPMP/EWP/633/02 Rev 2)

recently revised

- In particular, to minimize the risk of functional monotherapy in heavily pretreated patients

- End of consultation : 30 April 2008 (comments to be sent to EWPSecretariat@emea.europa.eu)

EMEA Guidelines on anti-HIV drugs
Heavily pretreated patients

- Treatment goal to achieve <50 copies/ml
- Need to distinguish :
  - Patients with various treatment options at time of treatment failure GSS≥2
  - Patients with few or no licensed therapeutic options at time to treatment failure

Patients with remaining options (GSS ≥ 2)

- Several possible comparative designs
  - Superiority trial : such as OBT + Test vs OBT
    %<50 copies/ml at week 24, follow-up 48 weeks
  - Non inferiority trial
    Justification of the non inferiority margin, longer efficacy data, low lost to follow up
    (Problem of the mix comparator (CPI) for Resist trials with TPV/rtv, originally designed as non inferiority)

Patients with few or no remaining options (GSS <2) 1/2

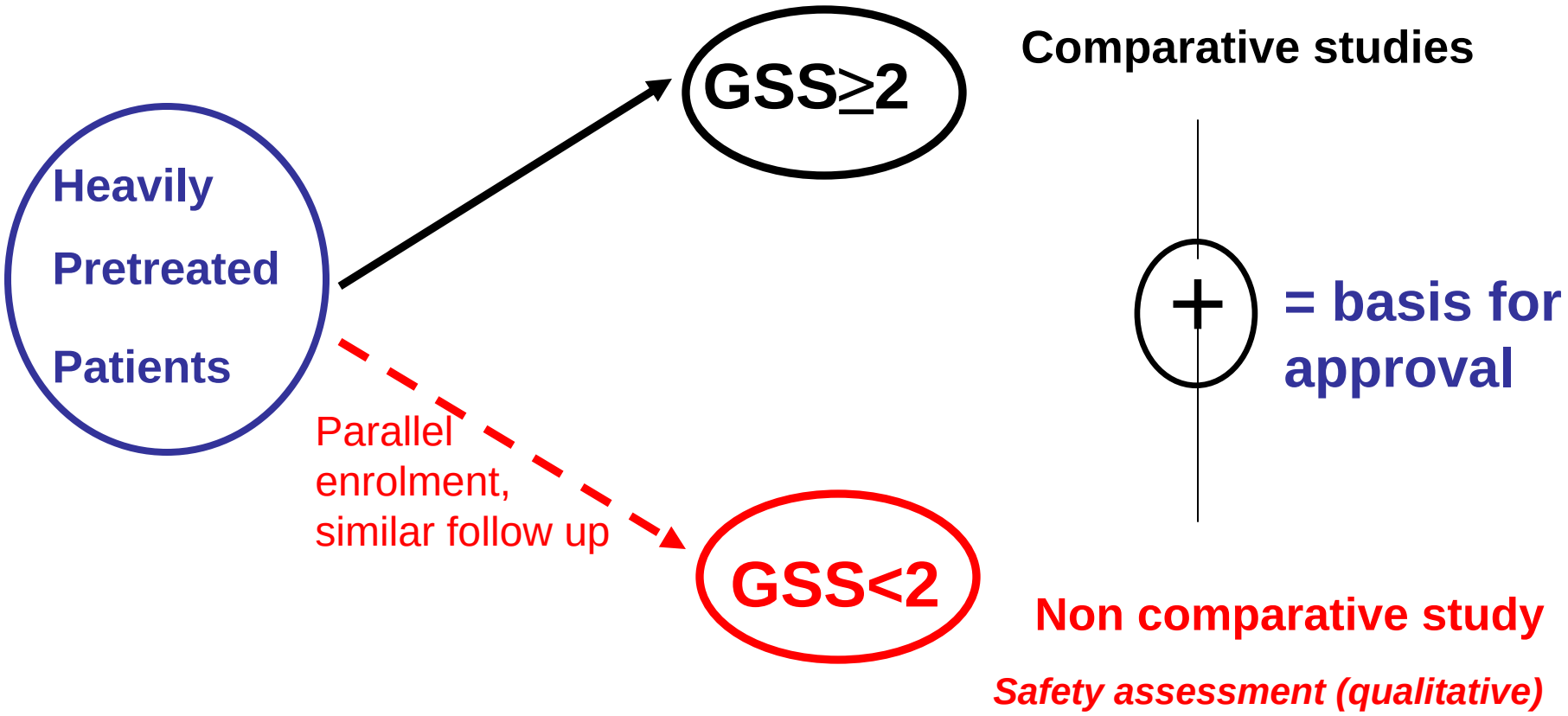
- *« If there are convincing data as regards the magnitude of the treatment effect and durability of response from comparative studies conducted in less heavily pre-treated patients, this may form the main basis for a submission. The rational being that data derived from such studies delineates the efficacy potential for the compound as well as long term safety under well-controlled conditions »*

- *« After screening for inclusion, there will be patients who are ineligible for randomisation because they have less than two likely active licensed drugs available for use in OBT. These patients could be included in a parallel arm of the study in which they receive the novel agent plus OBT (including another experimental compound). Such patients should be followed in the same manner as those in the randomised arms of the study with the primary aim to provide safety data.*

Patients with few or no remaining options (GSS <2) 2/2

- *Parallel* enrolment of patients in deep salvage GSS <2 in *non comparative* studies
  - Answer to a medical need
  - Contributive (qualitative) descriptive safety data

EMEA RECOMMENDED APPROACH



OVERALL

- Regulatory requirement : need for adequate efficacy / safety for doing a proper benefit/risk assessment => need for *comparative* study
- Need fo avoid functional monotherapy => regulatory requirement and clinical practice might not be compatible for GSS=0, 1
- However, non comparative studies might be *supportive* for *safety* assessment (*qualitative* information) in these patients
- Extrapolation of *efficacy* data from less experienced to GSS=0 or 1 has to be assumed