Justifying a Noninferiority Margin

Approaches from DAVP

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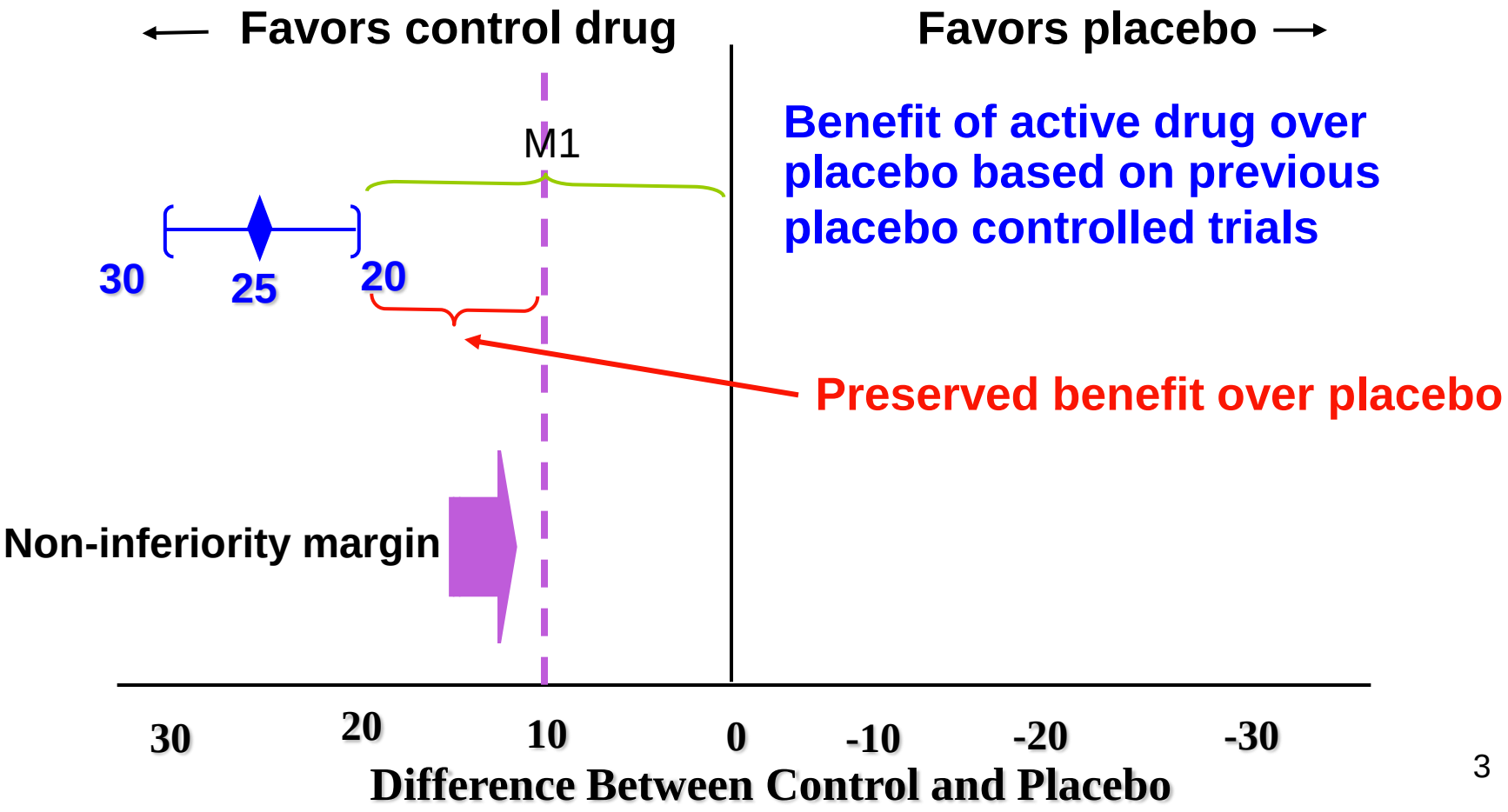
N.I. Clinical Trials

- Draft Guidance dated 2/26/10
- Not as good as superiority studies
  - "This design is chosen when it would not be ethical to use a placebo"
  - "superiority trial… is entirely interpretable without further assumptions"
  - "NI study is dependent on knowing something that is not measured in the study, namely, that the active control had its expected effect in the NI study"
- NI study relies on outside information to justify margin
  - "the critical problem, and the major focus of this guidance is determining M1... It must be estimated (really assumed) based on past performance of the active control and by comparison of prior test conditions to the current test environment."
  - "Determining the NI margin is the single greatest challenge in the design, conduct, and interpretation of NI trials."

NI: Determining a margin

Quantifying the Effects of a Control Drug



NI: Margin justification

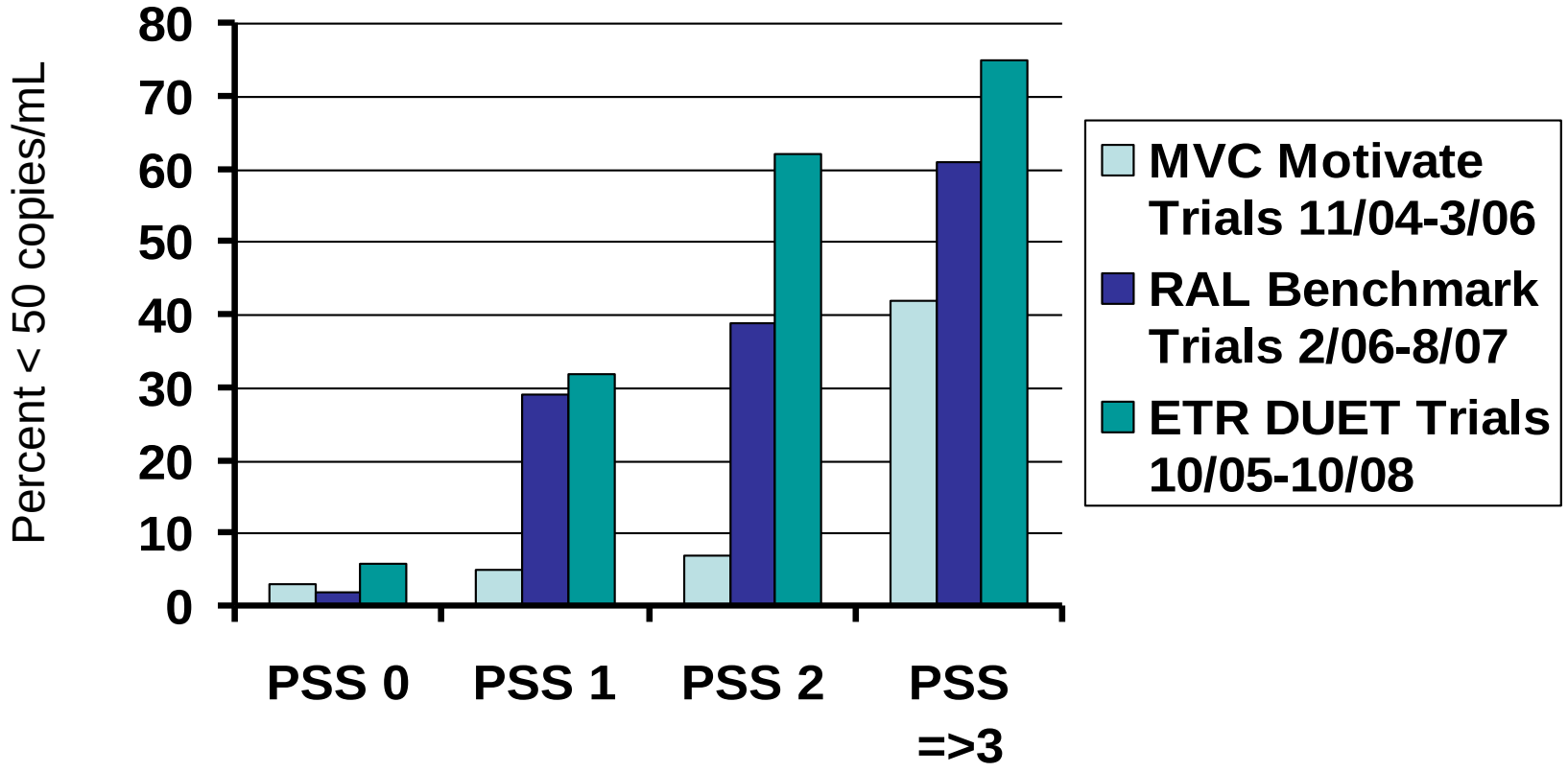
Should address

1. The effect size of the control drug (what the test drug is replacing) in the setting of the planned trial
2. An evaluation of the constancy of the effect of the control drug in the current trial

NI: Margin justification (cont)

- The constancy assumption will likely be invalid due to NI vs. historical trial difference in:
  - Baseline patient characteristics (PSS, CD4, VL)
  - Background drugs taken
  - Variation in response rates
- In order to make sure NI margin is valid
  - New NI trial design should mimic the original superiority trial for the active control drug as close as possible (Inclusion/exclusion, endpoints)
- NI margin needs to
  - take variability into account by preserving a certain percentage of the active control's effects, (e.g, 50%)

Virologic Response (HIV-RNA < 50) for OBT over Trials/Time



Phenotypic Susceptibility Score

Raltegravir Example

Conduct NI trial in one PSS category the margin is as follows:

PSS Score	Treatment Difference (%)	95% LB	95% UB	Margin (%)
0	49	35	62	18
1	34	23	45	12
2	30	18	41	9
$\geq$ 3	10	-7	27	0

Lower PSS score leads to better margin

Raltegravir Example

Mixture of PSS Score (% of patients with PSS=0, 1, 2, ≥ 3	Tx Difference (%)	95% LB	95% UB	Margin (%)
17%, 32%, 31%, 20%	31	23	38	12
Exclude PSS ≥ 3 25%, 50%, 25%, 0%	36	28	44	14
Only enroll PSS =1 or 2	32	22	42	11

No ETV or MVC use –

DRV use ranged 34% (trial 018) – 50% (trial 019)

Etravirine Example

Mixture of PSS Score (% of patients with PSS=0, 1, 2, ≥ 3	Tx Difference (%)	95% LB	95% UB	Margin (%)
16%, 37%, 28%, 19%	23	17	29	8
Exclude PSS ≥ 3 25%, 50%, 25%, 0%	36	28	44	12
Only enroll PSS =1 or 2				
0%, 50%, 50%, 0%	24	17	30	8
0%, 75%, 25%, 0%	27	20	35	10
0%, 25%, 75%, 0%	20	12	28	6

All patients received DRV

No raltegravir or MVC use

Maraviroc BID Example Week 48

Mixture of PSS Score (% of patients with PSS=0, 1, 2, ≥ 3	Tx Difference (%)	95% LB	95% UB	Margin (%)
13%, 25%, 26%, 36%	29	21	36	11
Exclude PSS ≥ 3 25%, 50%, 25%, 0%	35	28	43	14
Only enroll PSS =1 or 2				
0%, 50%, 50%, 0%	42	34	50	17
0%, 75%, 25%, 0%	40	31	49	15
0%, 25%, 75%, 0%	45	35	54	18

No DRV, ETV or RAL use in MVC arms

Estimated Sample Size Calculations

	Sample Size Requirement Based on the Assumptions										
Response	NI margin in % (Power=90%, α=0.025 one-sided)										
rate (%)	6	8	10	11	12	13	14	15	16	17	18
50			1051	868	730	622	564	467	410	364	324
55	2890	1625	1040	860	722	616	559	462	406	360	321
60	2802	1576	1009	834	700	597	543	448	394	349	311
65	2656	1494	956	790	664	566	488				
70	2452	1379	883	729	613	522	450				
75	2189	1231	788	651	547	466	402				
80	1868	1051	672	556	467	398	343				

Possible Solutions

- Attempts to match background therapies
  - Limit amount of specific drug or background use
  - Limit enrollment of patients with PSS=2

Patient/Investigator Acceptability??

Summary

- Defining noninferiority margin difficult
  - comparability of trials to establish margin (were patients similar)
  - changing availability of background drugs (does OBT differ from that used in previous trials?)
  - many will want to use raltegravir + darunavir as part of their OBT (a regimen not previously studied in randomized, controlled trials)
- Margins often only feasible (10-12% range) when majority of patients have GSS/PSS scores of 0 or 1.--- Difficult to enroll

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Back-up