Rolle von Wirksamkeitsnachweis und klinischer Relevanz im Rahmen der Zulassungsentscheidung

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Vizepräsident

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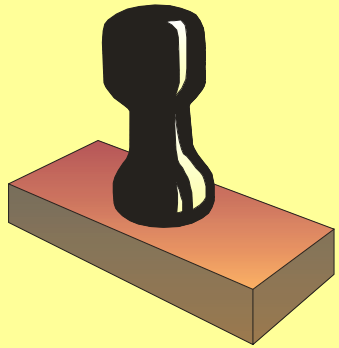
Gliederung

- Aufgaben des BfArM in der Arzneimittelzulassung
- Standards im Wirksamkeitsnachweis
- Nutzen-Risiko-Bewertung
- Efficacy vs. Effectiveness
- Ausblick

„Ideales Arzneimittel“

- *wirksam* unter experimentellen Studienbedingungen und im therapeutischen Alltag
- *verträglich* (ohne Nebenwirkungen)
- *sicher* (ohne gravierende Risiken)

- Zulassung erfolgt nach positiver Nutzen-Risiko-Bewertung



Aufgaben des BfArM nach AMG

- § 1
  - Qualität, Wirksamkeit und Unbedenklichkeit
- § 8
  - es dürfen keine Wirkungen oder Wirksamkeit beigelegt werden, die nicht nachgewiesen sind
- § 25
  - Nachweis von Wirksamkeit und Unbedenklichkeit nach dem gesicherten Stand der wissenschaftlichen Erkenntnis
- § 26
  - Arzneimittelprüfrichtlinien zur Konkretisierung

Regulatory Dilemma ...

Efficacy

Clinical Relevance

Comparative Effectiveness

Benefit-Risk-Assessment

Relative Efficacy

Early Access

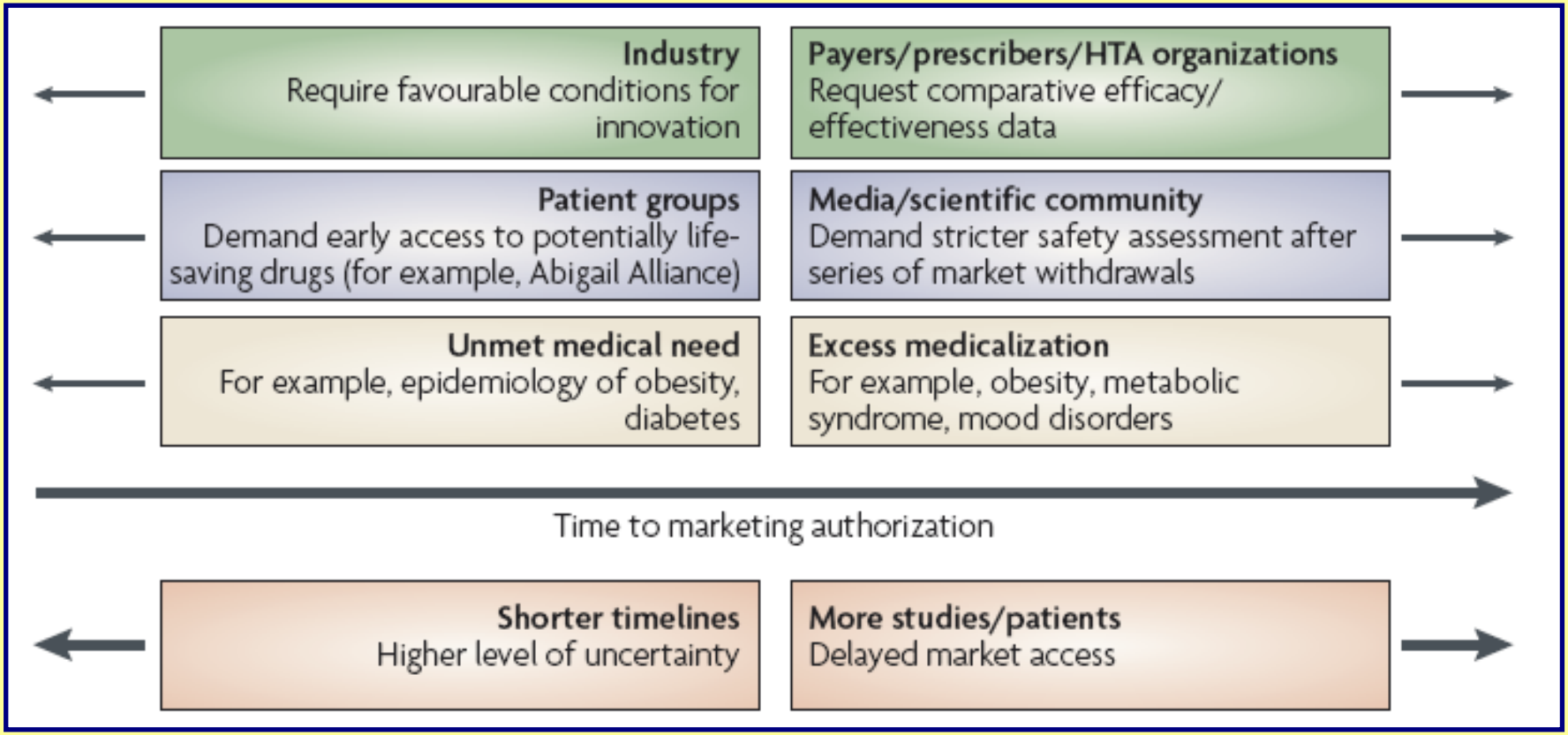
Risk Management

Effectiveness

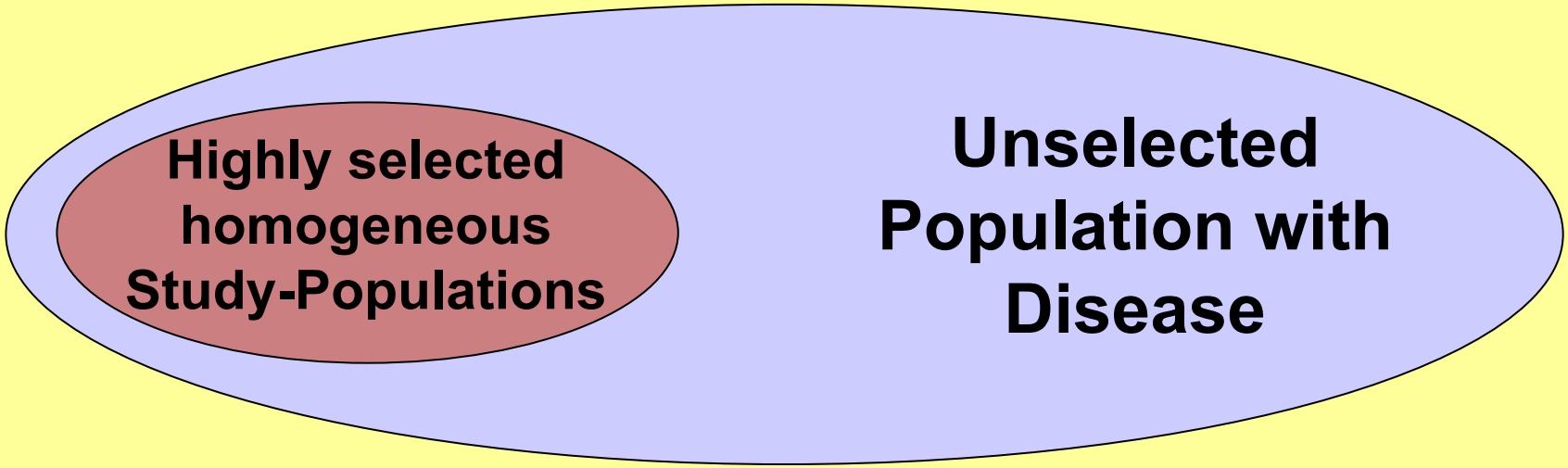
Cost Effectiveness

Regulatory Dilemma ...

from: Eichler HG et al., NRDD 2008



Study Populations in Clinical Trials



- Specificity >> Sensitivity
- Generalisability ?
- Labeling ?

Note for Guidance / Scientific Advice

- **Short-term Studies**
  - Placebo control
  - Three-arm-studies with active control and placebo
  - Duration
- **Maintenance/Long-term Studies**
  - Randomized withdrawal design (relapse prevention)
- **Endpoints**
  - Rating-scales
  - Means vs. responders
- **Specific Groups**
  - Severe forms
  - Elderly
  - Children and adolescents
  - Therapy-resistant patients
  - Negative or cognitive symptoms

Plazebo-kontrollierte Studien

Vorteile	Nachteile
•ermöglicht Abschätzung der Assay-Sensitivität und damit interne Validierung der Studie	•evtl. erhöhtes Risiko durch „Nichtbehandlung“
•Abschätzung der klinischen Relevanz besser möglich	•Verzögerung der Behandlung
•Stichprobenumfang geringer	•evtl. stärker eingeschränkte Generalisierbarkeit der Ergebnisse auf die Grundgesamtheit
•Rekrutierung schneller	
•Studienkosten geringer	

Aktiv-kontrollierte Studien

Vorteile	Nachteile
•Daten zu relativer Wirksamkeit und Verträglichkeit	•wegen fehlender Assay-Sensitivität Risiko falsch positiver Studien
•zumindest theoretisch keine inaktive Behandlung	•Äquivalenz/Nicht-Unterlegenheit nicht als Wirksamkeitsnachweis geeignet
•weniger Therapieabbrüche wegen mangelnder Wirksamkeit	•aktiver Komparator evtl. kein Therapiestandard
•evtl. eher akzeptabel bei Ethik-Kommissionen	•mehr Therapieabbrüche wegen unerwünschter Wirkungen
	•Tendenz Wirksamkeitsunterschiede zu minimieren
	•Stichprobenumfang größer
	•höhere Studienkosten

Short-term Studies in Schizophrenia

- Parallel, double blind, randomized and controlled trials necessary
  - in general 6 week duration
- Choice of control
  - Placebo
  - Active comparator
  - Fixed dose studies
  - Choices must be justified by the applicant
- Three-arm or multi-arm studies preferred
  - Assay sensitivity

Study Designs in Schizophrenia

- **Three adequate and well controlled designs possible:**
  - **Placebo control** — **Superiority**
  - **Dose comparison** — **Superiority**
  - **Active control** — **Superiority or Equivalence/Non-Inferiority**

- **Non-Inferiority Design tested in most cases**
  - **New drug is not inferior by more than some predefined amount** ➔
  - **Non-Inferiority Margin**
    - **To define this margin „assay sensitivity“ has to be known**

Short-term Studies

PANSS Total Score; Model-Based Mean Change from Baseline at Endpoint; LOCF Data Set, Efficacy Sample; Key Phase III, Short-Term, Placebo-Controlled Efficacy Studies for Schizophrenia

	PANSS Total Score				
Protocol/ Treatment	N	Baseline	Change from Baseline	Treatment Difference (95% CI) versus Placebo	P-Value
31-97-201 (4-week study)					
Placebo	102	100.9	-2.9	--	--
Haloperidol 10 mg	99	99.9	-13.8	-10.8 (-17.2, -4.5)	0.0008
Aripiprazole 15 mg	99	98.8	-15.5	-12.6 (-18.9, -6.3)	0.0001
Aripiprazole 30 mg	100	99.6	-11.4	-8.5 (-14.7, -2.2)	0.0089
31-97-202 (4-week study)					
Placebo	103	94.1	-5.0	--	--
Risperidone 6 mg	95	92.6	-15.7	-10.7 (-16.6, -4.9)	0.0004
Aripiprazole 20 mg	98	93.5	-14.5	-9.6 (-15.4, -3.8)	0.0013
Aripiprazole 30 mg	96	91.6	-13.9	-8.9 (-14.8, -3.1)	0.0029
CN138-001 (6-week study)					
Placebo	107	92.6	-2.3	--	--
Aripiprazole 10 mg	103	92.9	-15.0	-12.7 (-19.0, -6.4)	0.0001
Aripiprazole 15 mg	103	92.4	-11.7	-9.4 (-15.7, -3.1)	0.0036

Short-term Studies

Table 10: Treatment assignments in the four short-term phase III studies.

	Treatment Group						
		ER OROS Paliperidone (mg/day)					Olanzapine
	Placebo	3 mg	6 mg	9 mg	12 mg	15 mg	10mg/day
Key Efficacy Studies in Subjects at Least 18 years of age with Schizophrenia							
R076477-SCH-303	X		X	X	X		X
R076477-SCH-304	X		X		X		X
R076477-SCH-305	X	X		X		X	X
Safety and Tolerability Study in Elderly Subjects with Schizophrenia							
R076477-SCH-302	X	3 mg to 12 mg/day					Not Included

Assessment of Efficacy in Short-term Studies of Schizophrenia

- **Statistical Significance *and* Clinical Relevance needed**
- **Endpoints:**
  - **Primary: PANSS or BPRS**
  - **Secondary: CGI**
- **Difference between Baseline and Post-Treatment-Score**
- **30 % Improval on Standard Ratings is Considered Clinical Relevant**

Responder Analysis: 30% improvement in PANSS-Scores

In the responder analyses significantly more responders were observed in all paliperidone groups (56%, 51% and 61% in the 6 mg, 9 mg and 12 mg groups, respectively, $p<0.001$ for all doses) compared to the placebo group (30%).

In the responder analyses significantly more responders were observed in both paliperidone groups (50%, $p=0.025$ and 51.4%, $p=0.012$ in the 6 mg and 12 mg groups, respectively) compared to the placebo group (34.3%).

In the responder analyses significantly more responders were observed in all paliperidone groups (40%, 46% and 53% in the 3 mg, 9 mg and 15 mg groups, respectively, $p<=0.001$ for all doses) compared to the placebo group (18%).

Maintenance of Effect

- Short-term effects should be maintained during the episode
- Randomized withdrawal study (relapse prevention study) is the preferred design
- Duration: at least 6 months
- Placebo-controlled extension study possible alternative, but not preferred

Randomized Withdrawal Study

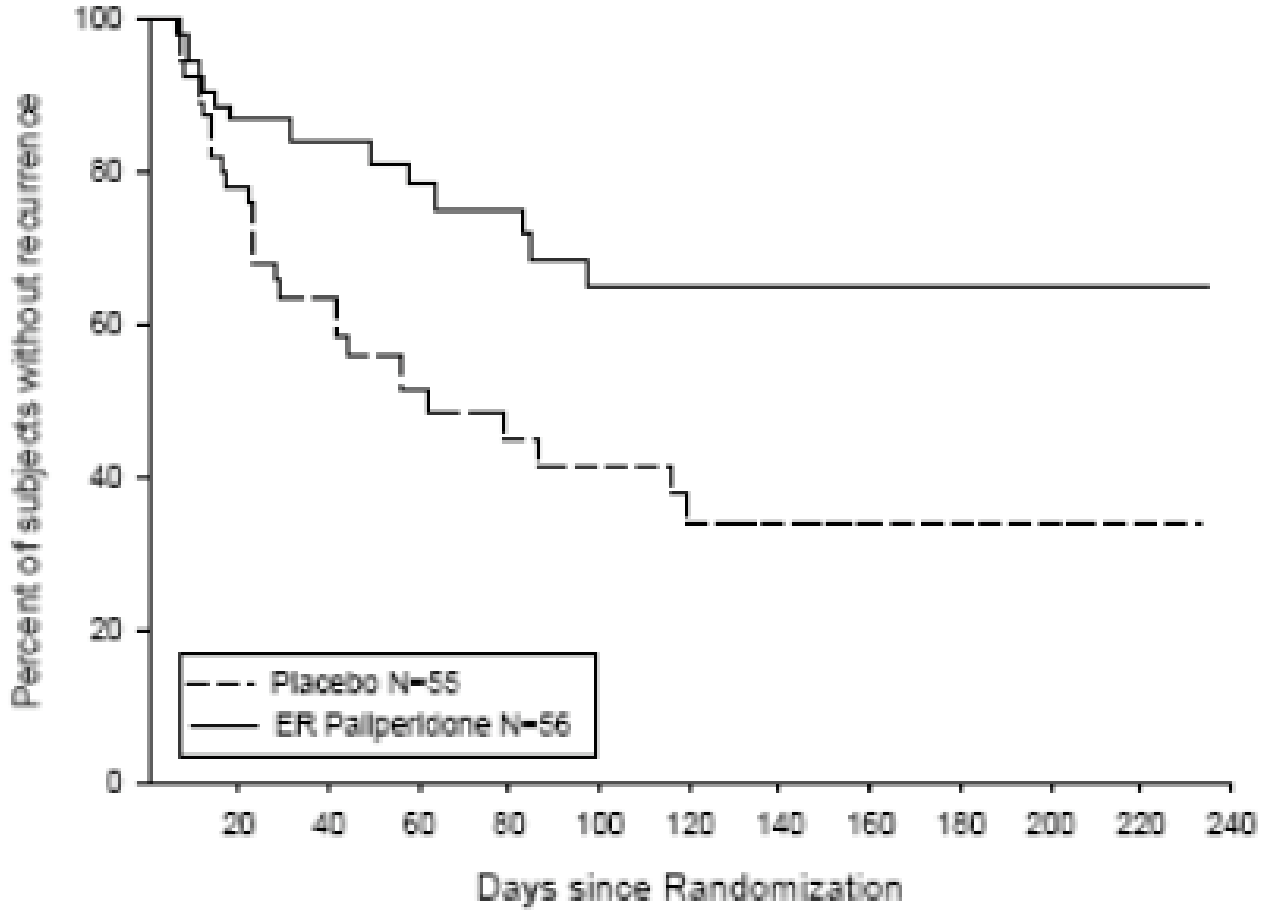
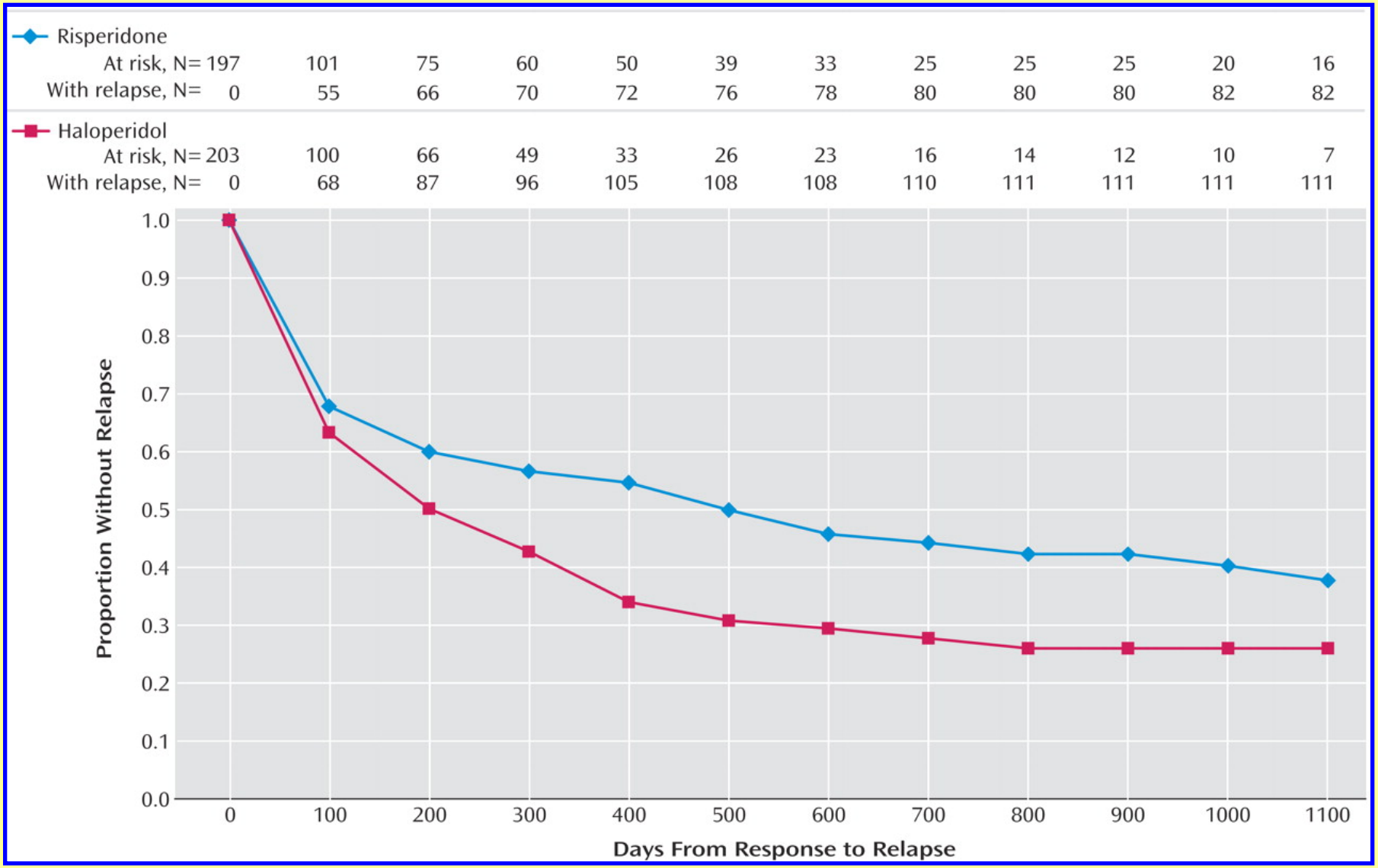


Figure 12: Time to recurrence in Study SCH-301. ITT population, interim analysis.

Randomized Withdrawal Study



Schizophrenia: *Negative* or *Cognitive* Symptoms as Target for a Drug Treatment Claim

- **Both are considered as domains**
  - with an unmet medical need
  - which are not „pseudospecific“, but phenomenologically distinct from other symptoms
- **Overlap between these domains**
  - More data needed
  - Overlap would weaken possibility of separate claims
- **Do negative or cognitive results respond differently to standard antipsychotics**
  - In both domains results are disappointing

Schizophrenia: *Cognitive* Symptoms as Target for a Drug Treatment Claim

- **Population:**
  - Distinct „Cognitive Impairment“ in patients with schizophrenia should be further established
  - Generalizable to community
- **Phase of the illness:**
  - In stable residuum
- **Domain:**
  - Spectrum of cognitive symptoms as a single target clearly preferred (MATRICS; CNTRICS; CANTAB; BACS a.o.)
  - Not enough data to focus on specific subtypes/targets
- **Co-Primary Endpoint:**
  - Functional outcome mandatory

Functional Outcome as Co-Primary Endpoint

- **Validated instruments for this population:**
  - Yet no ideal instrument available
  - Transferable to „real world“ in the community
  - Cross-cultural adaptability
- **Design Issues:**
  - Broad spectrum agents vs. narrow target
    - „add-on“ vs. „monotherapy“
  - Choice of control group
    - Placebo
    - Active control
  - Study duration
    - 6 months or longer
    - Maintenance of effect

Initial Severity and Antidepressant Benefits: A Meta-Analysis of Data Submitted to the Food and Drug Administration

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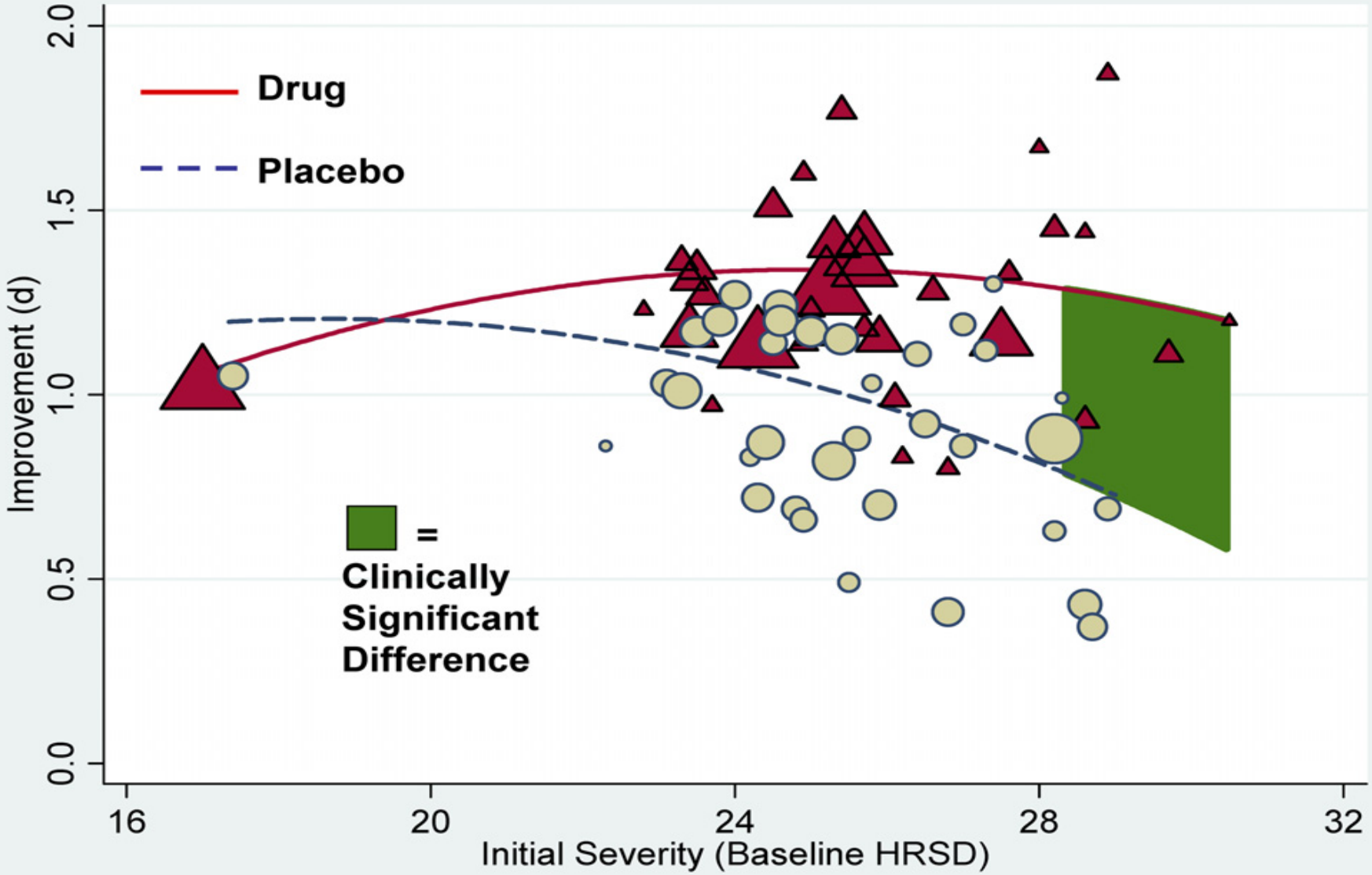
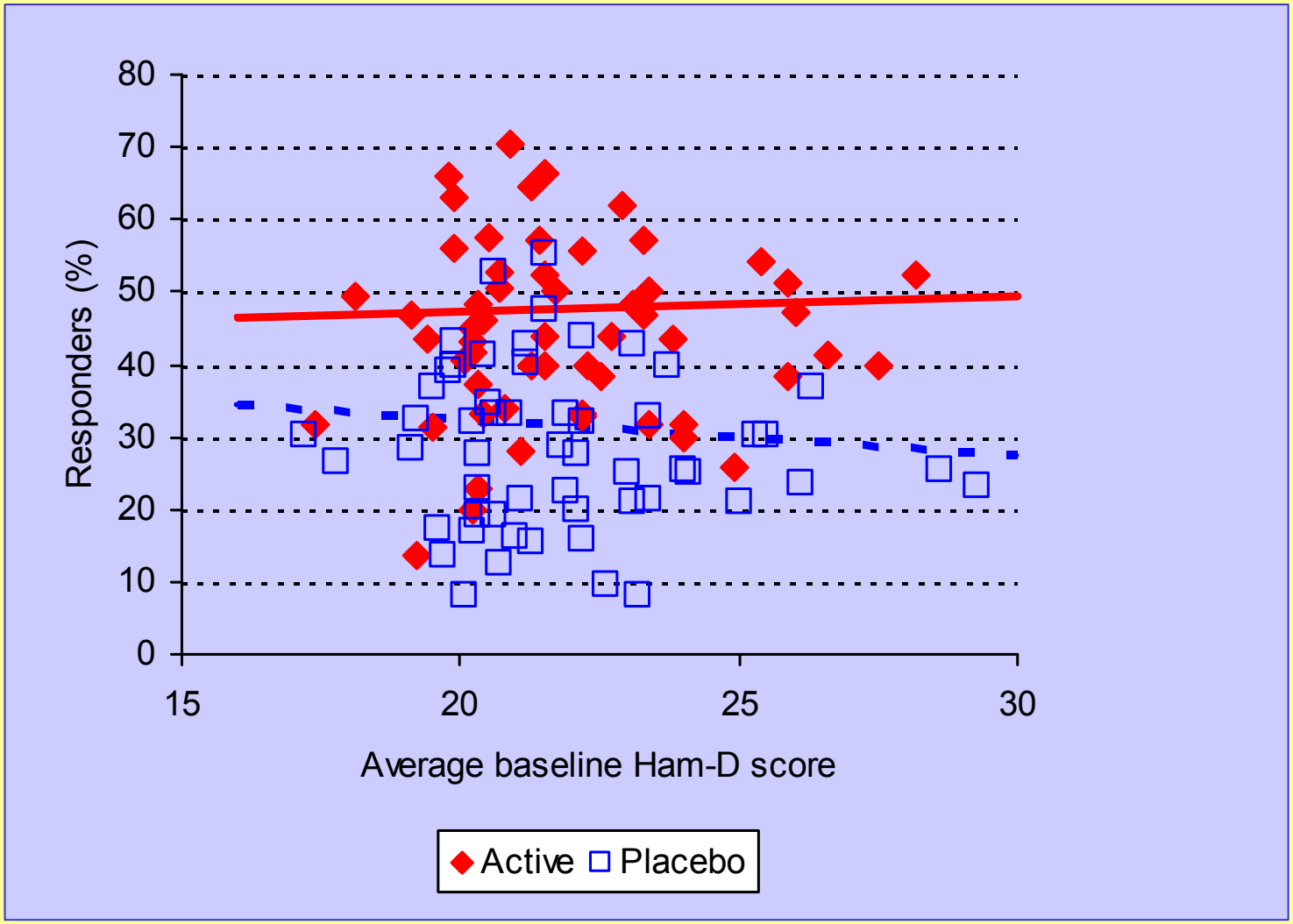


The placebo controlled database at approval for SSRIs and SNRIs (Melander H. et al.)

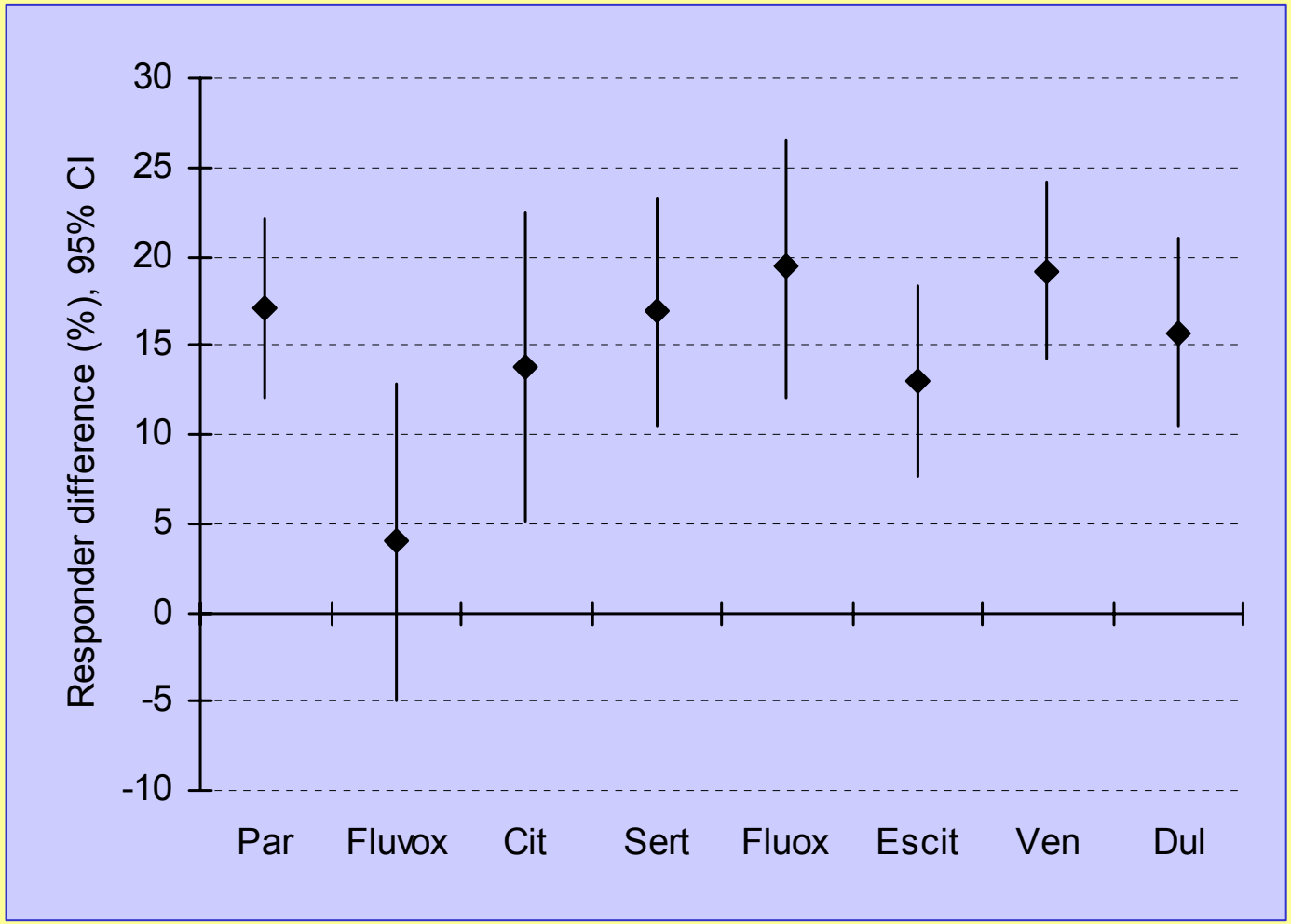
Substance	Year of submission	Number studies	Total number of patients	Average baseline Ham-D score Mean	Range
Paroxetine	1990	15*	1133	21.4	19.6; 24.1
Fluvoxamine	1989	5	409	22.6	19.7; 26.3
Citalopram	1992	5	485	23.8	22.7; 26.4
Sertraline	1993	4	914	23.2	20.5; 25.5
Fluoxetine	1984	8	553	22.0	19.3; 28.4
Escitalopram	2001	4	1181	21.2	19.5; 21,4
Venlafaxine	1992, 1996	9**	1493	21.4	19.5; 28.4
Duloxetine	2003	6	1242	19.8	17.6; 21.3
Total		56	7410	21.6	17.6; 28.4

*) One additional paroxetine study with 29 patients in total did not report responder results.
**) Immediate release formulation: 6 studies; Extended release formulation: 3 studies.

Responder rates (Melander H. et al.)



Overall difference in percentage of responders between active drug and placebo (Melander H. et al.)

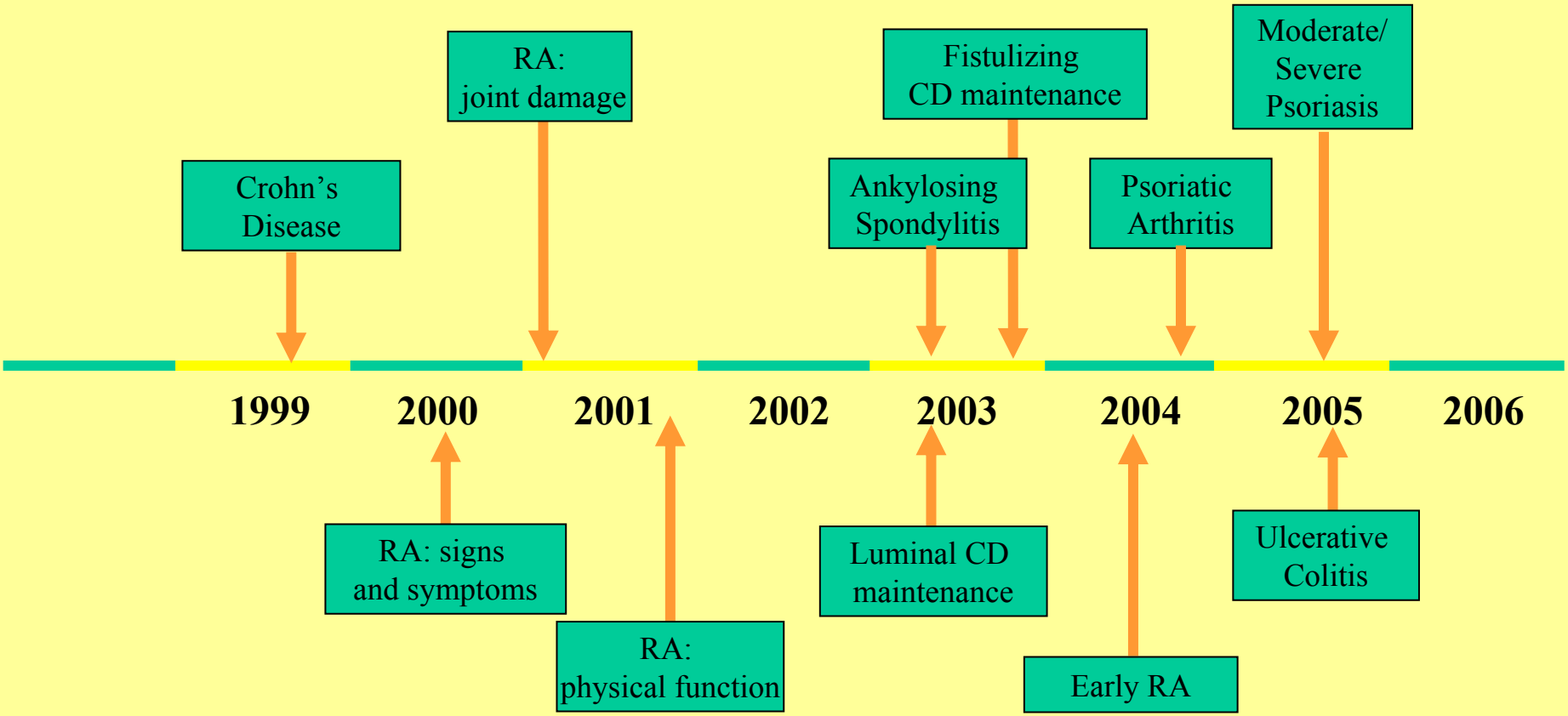


Rel. Efficacy Data already available...

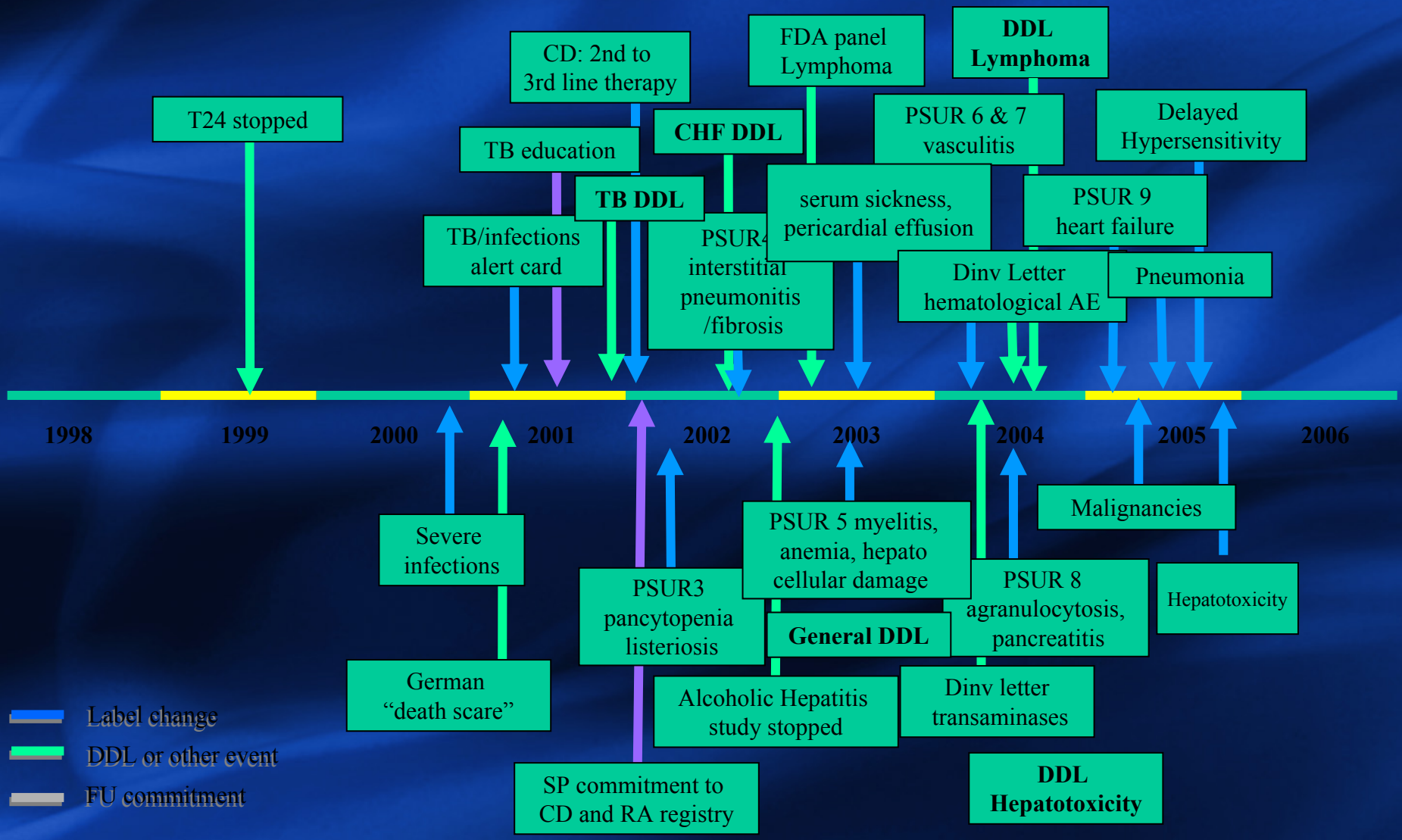
from: Eichler HG et al., NRDD 2010

Type of RE described	FDA medical review *n* out of 42 (%)	EPAR *n* out of 47 (%)
Active comparator trial of clinical efficacy in the medical review or EPAR	17 (40.5%)	24 (51.1%)
Active comparator trial of clinical efficacy in the label or SPC	13 (31.0%)	16 (34.0%)
Active comparator information on efficacy derived from an RCT with an active comparator and placebo group	2 (4.8%)	3 (6.4%)
Active comparator information on efficacy derived from an RCT with an active comparator group, but without placebo group	15 (35.7%)	21 (44.7%)
Superiority over active comparator was shown in a head-to-head RCT	1* (2.4%)	10* (21.3%)
Active comparator licensed in the relevant indication in the respective agency's jurisdiction?	15‡ (35.7%)	24‡ (51.1%)
Summary data of the active comparator trial(s) presented numerically (for example, mean, median, confidence intervals) in the medical review or EPAR	12 (28.6%)	24 (51.1%)

Evolution of Remicade (EU): Efficacy

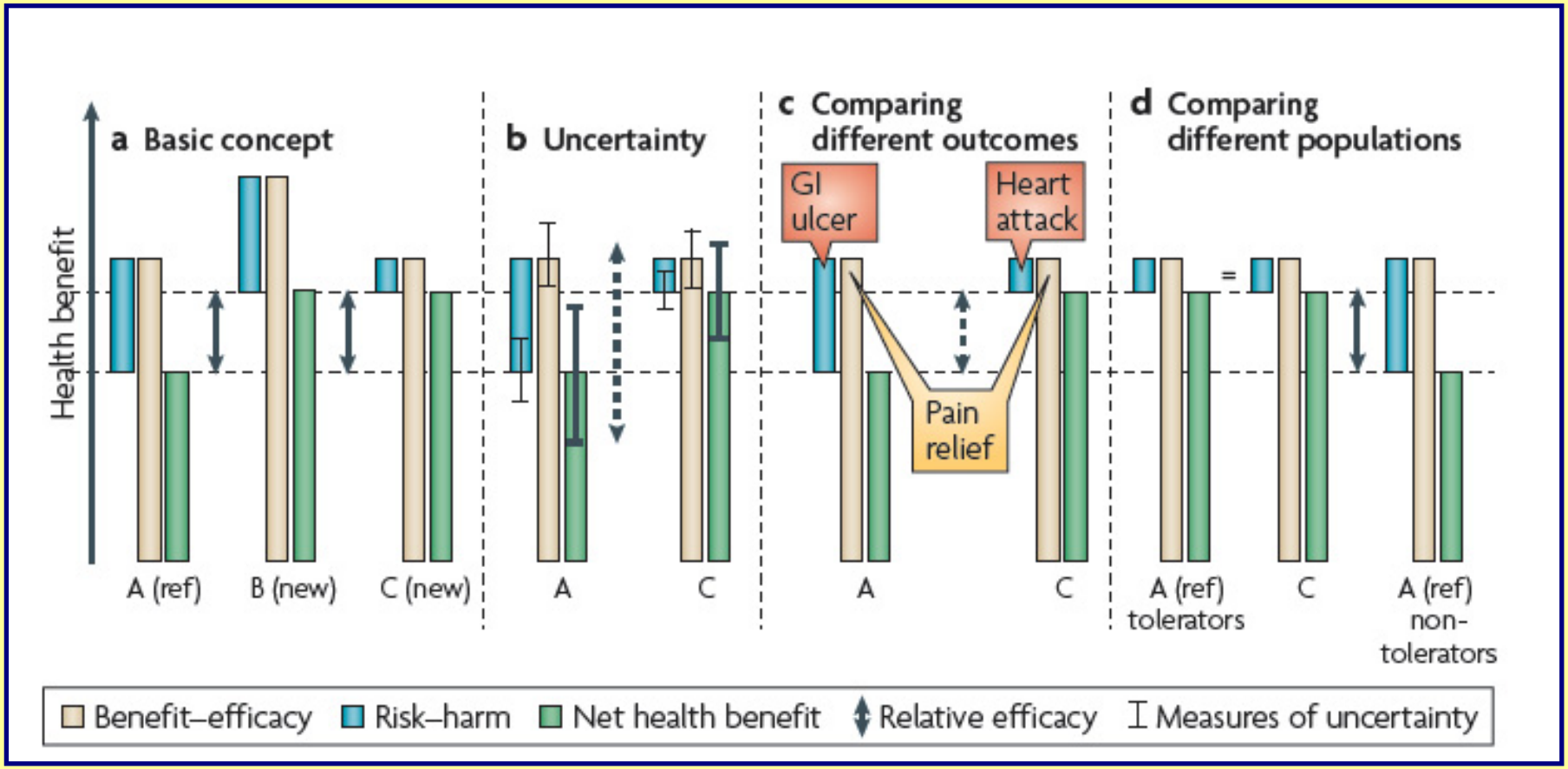


Evolution of Remicade (EU): Safety



Concept and possible pitfalls of relative efficacy assessment

from: Eichler HG et al., NRDD 2010



Wirksamkeit („efficacy“) vs. Nützlichkeit („effectiveness“)

- **„Efficacy“**
  - Reine Wirksamkeit einer Intervention unter kontrollierten Bedingungen

    Goldstandard: randomisiert, kontrolliert, doppelblind mit hoher interner aber niedrigerer externer Validität

- **„Effectiveness“**
  - tatsächliche Wirkung einer Intervention unter realen Praxisbedingungen mit niederigerer interner aber größerer externer Validität

- **Was können wir aus dem jeweiligen Ergebnis lernen?**

Effectiveness-Studien bei psychiatrischen Indikationen

- CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness):
  - Schizophrenie
  - Alzheimer Erkrankung
- STAR*D (Sequenced Treatment Alternatives to Relieve Depression)
- STEP-BD (Systematic Enhancement Program for Bipolar Disorder)

- CUtLASS (Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study)
- EuroSC (European Schizophrenia Cohort)
- SOHO (Schizophrenia Outpatient Health Outcomes)

Efficacy-Studien
aus regulatorischer Sicht

- **sind notwendig**
- **Efficiency-Studien sind ohne bekannte „assay sensitivity“ und wegen anderer methodischer Mängel nicht eindeutig interpretierbar**
  - **Fallzahlen !**
- **Grundlage für Zulassungsentscheidungen von BfArM, EMEA, und FDA weiterhin nur mit Efficacy-Studien als Gold-Standard !!!**
- **Projekt mit „quantitativen“ Bewertungsansätzen**

Possible Challenges ...

from: Eichler HG et al., NRDD 2010