Health Technology Assessment & Outcomes Research

AMNOG: 2 years

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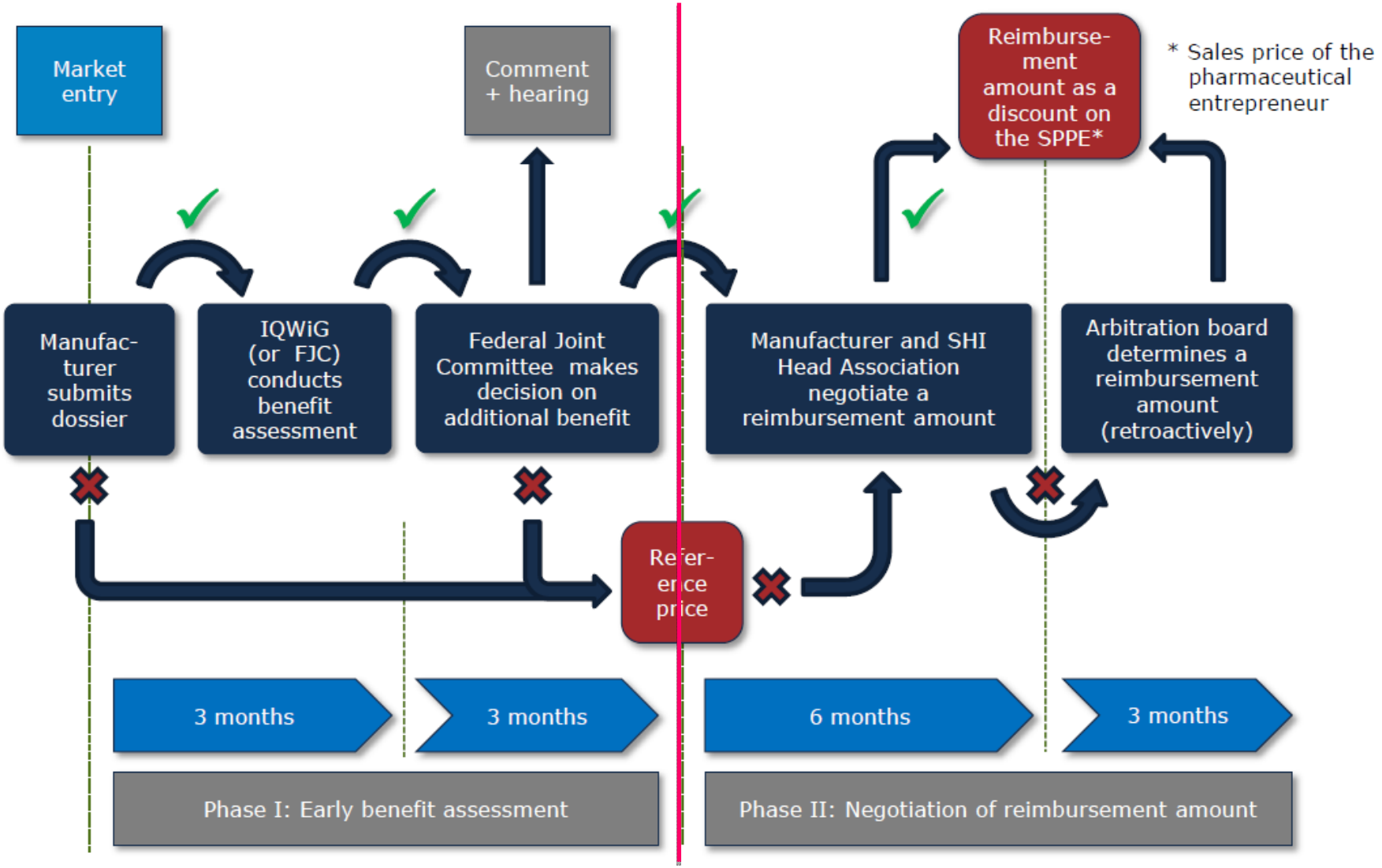
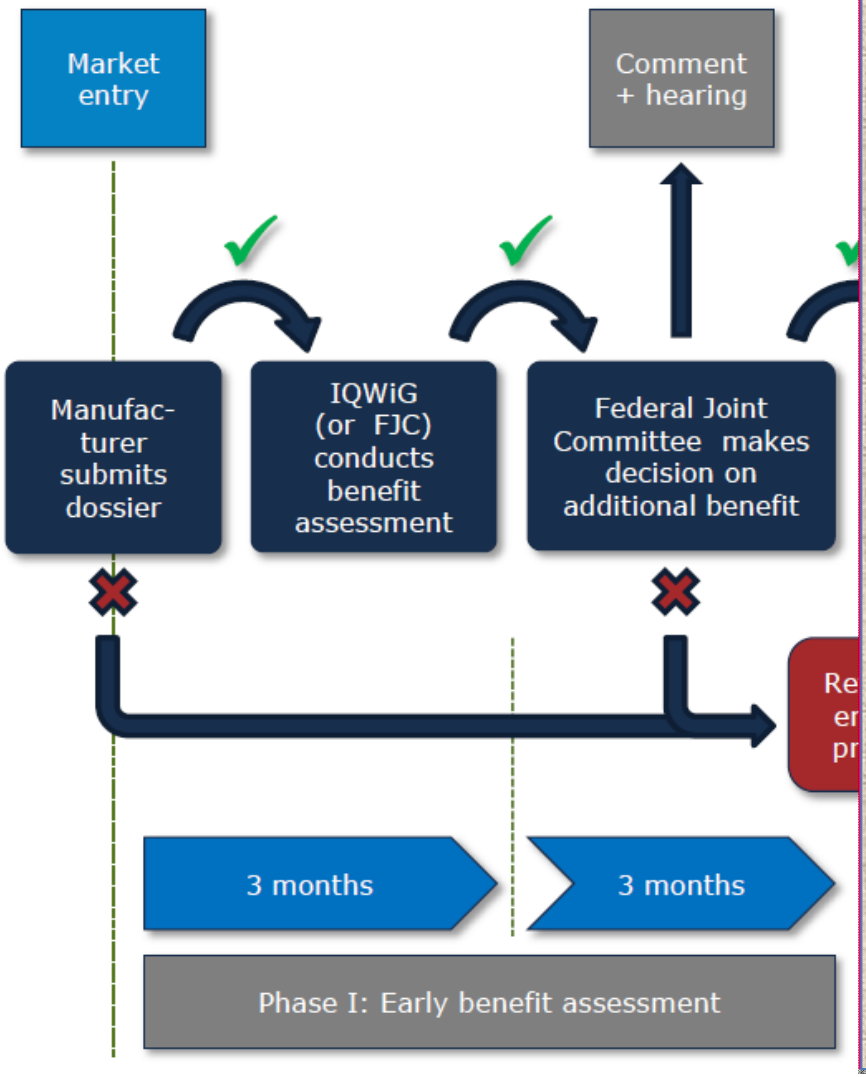
The AMNOG procedure



The AMNOG procedure



No additional Benefit

- **FRP**
- **Maximum Price is the Price of GBA Comperator (zVT)**

Additional Benefit

- **Price negotiation with GKV-SV**
- **No algorithm is known**
- **Price = f (extent of Benefit, certainity of benefit, Medical Need, European prices)+ε**

Key Questions

Is there an additional benefit against the GBA Comperator (zVT) proven?

Are there special patient groups with an additional benefit ?

How large is the benefit ?

How certain are the conclusions ?

Assessment is Data Driven:

based on Clinical Data

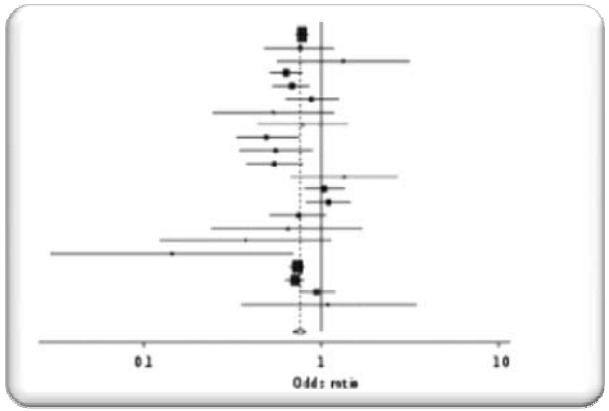
based on RCT Registration Studies

no economic Modelling

In some aspects more, in others, less rigorous than regulators

Pfizer

additional benefit vs GBA Comperator proven ?



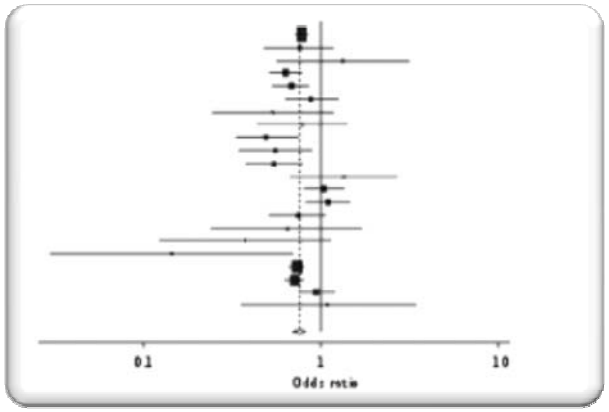
GBA Comperator (zVT)

- Possible to get advice from GBA
- will be determined by GBA according to the rules of Procedures
  - authorized for the indication
  - non-medicinal treatment: must be deliverable within the framework of the GKV
  - patient-relevant benefit has already been determined by G-BA
  - appropriate therapy in the therapeutic indication
  - more economic therapy
- Stratify Indications according to SMPC

Example: Axitinib in Renal Cell Cancer

- Stratified Randomization according 1st line treatment.
- Study Comperator for both arms: Sorafinib
- GBA zVT Cytokine pretreated pts: *Sorafnib*
- GBA zVT: Sunitinib pretreated pts: *Everolimus*
- No H2H – No Indirect comparison is possible ➔ no additional benefit

additional benefit vs GBA Comperator proven ?



Patient relevant Endpoints

- Mortality, QoL,Morbidity
- Validated Surrogates are required
- IQWiG Rapid Report
- Composite endpoint may be questionable
- Reanalysis is often required

additional benefit vs GBA Comperator proven ?

Example: Axitinib in Renal Cell Cancer

- **PFS is not accepted as patient relevant**
- **PFS is not seen as validated surrogate**
- **Reanalysis of Adverse Event data with Cox PH Model lead to an additional benefit**

Example: Apixban: Only symptomatic Deep Thrombosis are aceepted als patientreleavnt

SYMPTOMATIC DVT, n/N *	3/1528	7/1529
EVENT RATE (%)	0.20	0.46
ASYMPTOMATIC DVT, n/N **	139/968	236/990
EVENT RATE (%)	14.36	23.84

Primary endpoint of the Study

Pfizer

Are there special patient groups with an additional benefit ?

Subgroup analysis to identify Effect Modifier is required.

Data may not be pooled.

The Indication is often stratified by GBA according to SMPC

- **For every subindication different comperator possible**
- **For every Comperator benefit has to be proven (slicing)**

Reanalysis is required.

Are there special patient groups with an additional benefit?

Example : Xalkori for ALK positive patients in NSCLC

GBA ECOG 0-2 ZVT is Chemotherapy
ECOG 2-4 ZvT is BSC

Study Data for ECOG 0 to 2

Example : Xiapex for Dupytren
RCT vs Placebo Injection

GBA sliced according severity
For every sliced a comparator was chosen
Surgery
Needle facetomie
No treatment

Beside Power issues, no adjusted indirect Comparison was possible

Early Benefit Assement

How certain are the conclusions ?

Prove:

at least to significant, well conducted RCTs

***Indication*:**

one well conducted RCTs

several studies with modest certainity

Hint:

one study with modest certainity, several studies with minor certainty-

adjusted indirect comparison

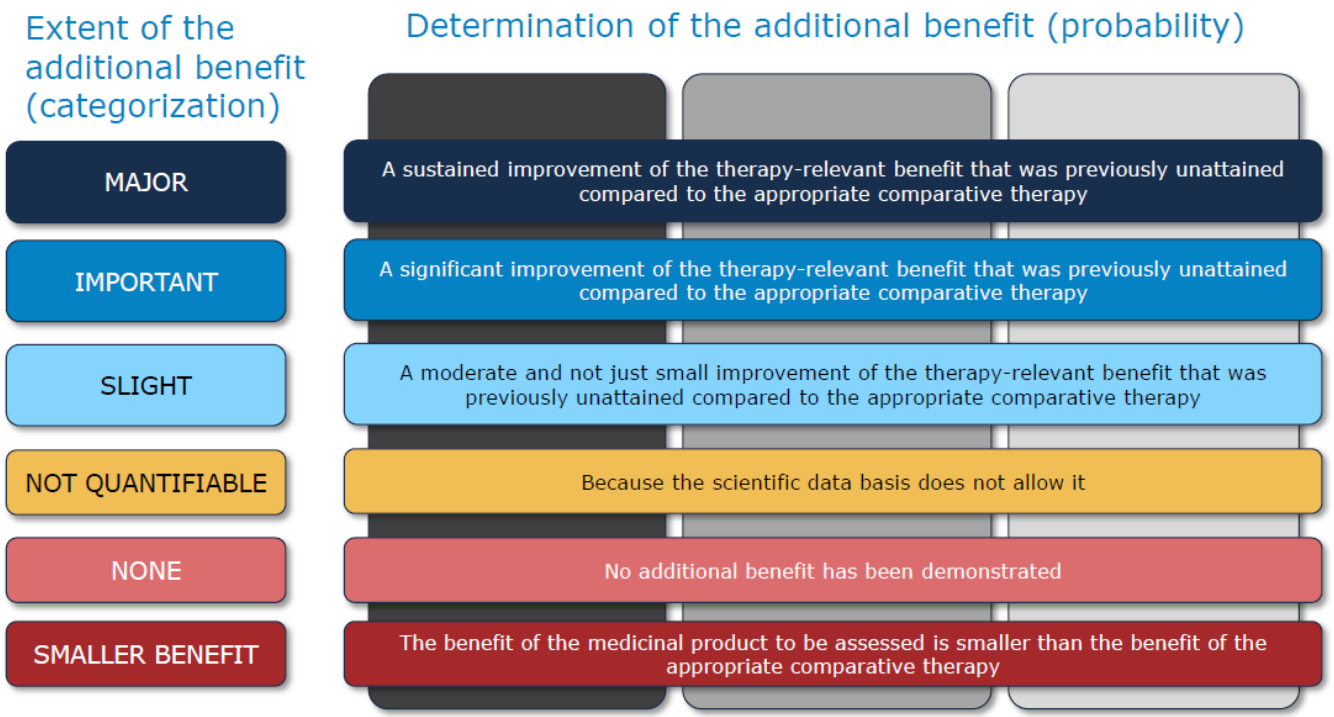
H2H Trial are prefered

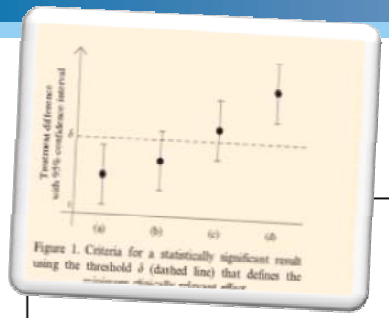
Downgrading:

- **Adjusted Indirect Comparison and MTC are a fall back option**
- **Extensive Study and Endpoint assessment concerning possible bias may lead to downgrading**

How large is the Benefit- AMNOG

Differentiation of the additional benefit





How large is the Benefit: IQWiG Proposal

		Target figure category			
		Survival time (mortality)	**Severe** symptoms *(or consequential complications)* and side effects	*Quality of life*	**Non-severe** symptoms *(or consequential complications)* and side effects
Added benefits	**Considerable** **Lasting major improvement of therapy-relevant benefits thus far not attained as compared to the feasible comparison therapy**	Considerably lengthened survival **CI_S: 0.85** (RR_1 = 0.50)	Long-term freedom or largely avoiding **CI_S: 0.75** (RR_1 = 0.17) **and risk ≥ 5%**[2]	*Considerable improvement*[1] **CI_S: 0.75** (RR_1 = 0.17) **and risk ≥ 5%**[2]	Not occupied
	Significant definite improvement **of therapy-relevant benefits** thus far not attained **in comparison** to the feasible comparison therapy	Moderately lengthened survival time **CI_S: 0.95** (RR_1 = 0.83)	Reduction or relevant avoidance **CI_S: 0.90** (RR_1 = 0.67)	*Significant improvement*[1] **CI_S: 0.90** (RR_1 = 0.67)	Significant avoidance **CI_S: 0.80** (RR_1 = 0.33)
	Slight moderate and not only slight improvement **of therapy-relevant benefits** thus far not attained as compared to the feasible comparison therapy	*Any (statistically significant) lengthened survival* **CI_S: 1.00**	*Any (statistically significant) reduction* **CI_S: 1.00**	*Relevant improvement*[1] **CI_S: 1.00**	Relevant avoidance **CI_S: 0.90** (RR_1 = 0.67)

Upper limit of 95% Confidence Interval has to be lower than a certain margin

Additions as compared to A

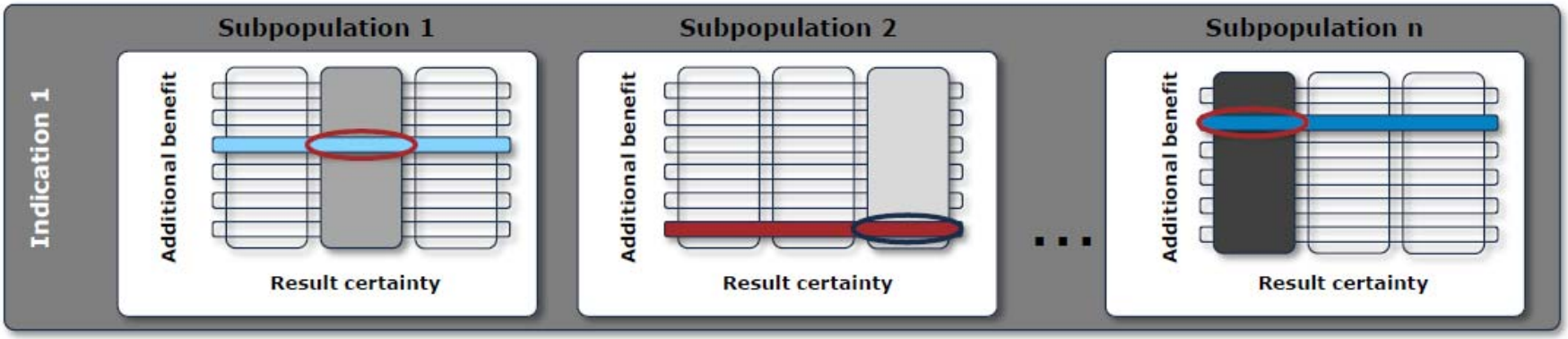
1: The prerequisite is the u

2: for at least one of the two groups being compared.

AM-NutzenV: Medication benefits evaluation regulations, CI_S: Threshold parameter for the upper limit of the 9[illegible] confidence interval, RR_1: actual relative risk

Devolped under the assumption of 2 RCT

Complex assessment grid: G-BA decision is differentiated according to therapeutic indication, subpopulation, additional benefit category and result certainty



IQWiG summarized all assessments to one assessment for the Subpopulation

This is a proposal for the GBA appraisal

GBA may come to other extents

Example: Axitinib in Renal Cell Cancer (Cytokine pretreated pts)

IQWiG: hint for a considerable additional benefit

G-BA: indication for an slight additional benefit

Workshop bei der GMDS in Lübeck am 02.09.2013

„Methodische Aspekte bei der Nutzenbewertung von Arzneimitteln“

Organisation:
Dieter Hauschke, Claudia Schmoor, Ralf Bender, Friedhelm Leverkus

Benefit assessment of medical interventions: an international perspective,
Jost Kleinjen

Two example Dossier with Industry and IQWiG View

Asssesment Results

Status of the procedures (March 1, 2013)

Phase 1: Benefit assessment		Phase 2: Reimbursement	
Benefit assessment procedures	49	Set reimbursement amounts	19*
- Concluded	30	- Through negotiation	17
- Ongoing	19	- Through arbitration board	2*
Of these concerned with:		Ongoing procedures	6
- New therapeutic indication	3	- Negotiations	5
- Existing market	3	- Arbitration board	1
- Resubmission	1	Reference price classification	2
Waivers	3	Opt out	4

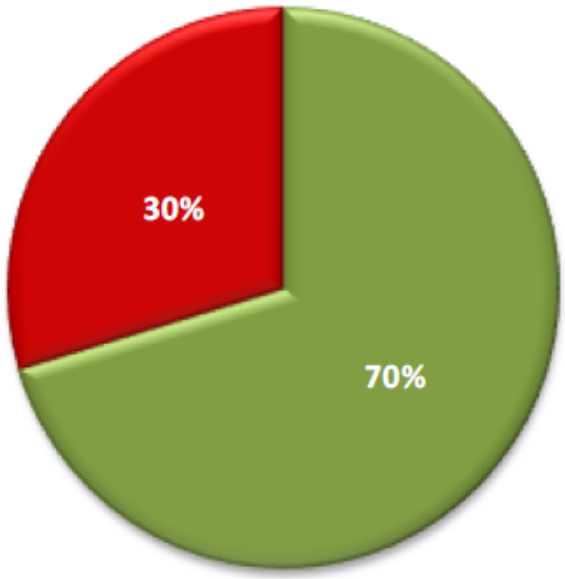
* one procedure is a special case of a parallel importer

Pfizer

1. Benefit assessment results: Many positive assessments …

Additional benefit for assessed active ingredients
(Federal Joint Committee's decisions, as of March 1, 2013)

27 active ingredients



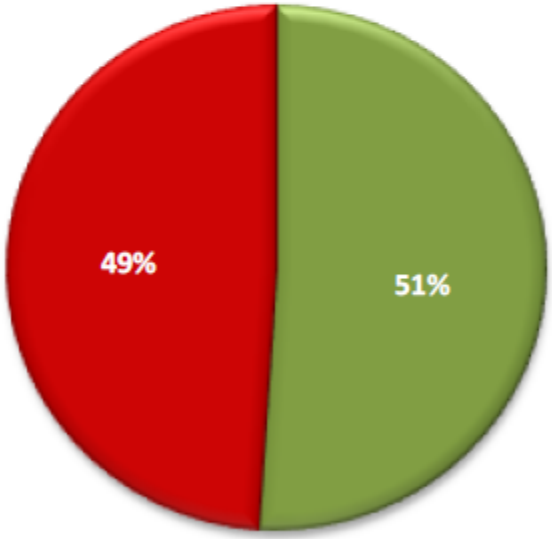
Additional benefit	Number	%
YES	19	70.4
NO	8	29.6
Active ingredients overall	**27**	**100**

* EXCLUDING bromfenac, pitavastatin, azilsartan (no dossier submitted)

1. Benefit assessment results: … for a few patient groups …

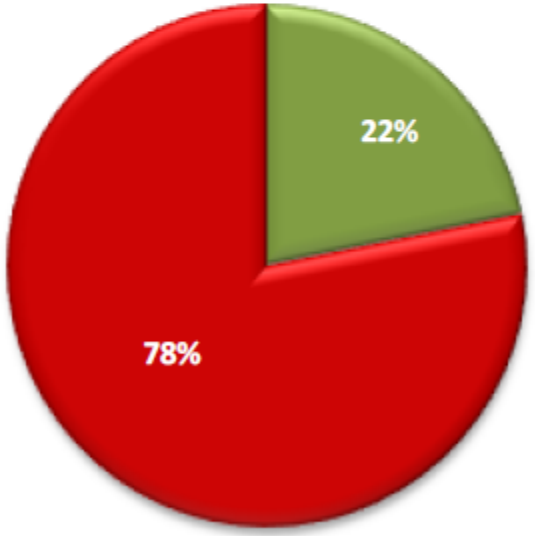
Evaluation based on subgroups and prevalences
(Federal Joint Committee's decisions, as of March 1, 20

45 Subgroups



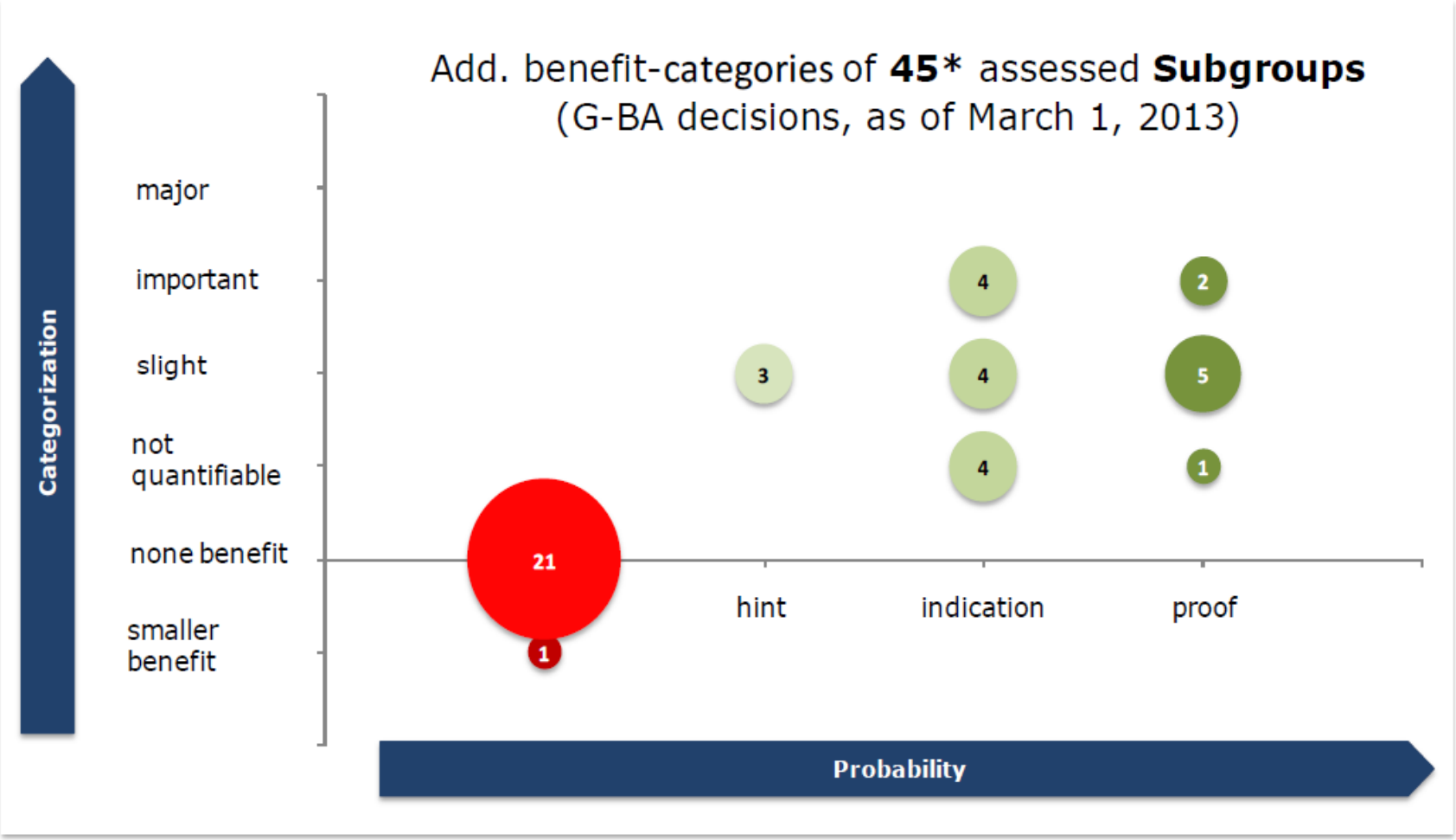
Additional benefit	Number	%
YES	23	51.1
NO	22	48.9
Subgroups overall	45*	100

2,680,922 patients



Additional benefit	Number	%
YES	585,022	21.8
NO	2,095,900	78.2
Patients overall	2,680,922	100

1. Benefit assessment results: … with many downgrades



Room for improvement

- **Choice of zVT**
  - Orientation at the „best therapy“
  - Best available evidence
  - Closer Co-operation with regulatory bodies and industry
- **Validation of Surrogate Endpoints is very strict**
- **Take into account situation with 1 Study**
- **Slicing and Subgroup Analysis reduces the Power**
- **No data – No evidence**
  - Interpolation- Regulatory Decision- Grade 8 indirectness
- **Weighting of different endpoints with e.g. DCE should discussed**

Welcome in the New World

- Economic Modelling plays no role
- Biometric expertise is essential in developing the dossiers
- The assessment methods differ from ICH
- Experts for IQWiG assessments are in the country
- Reanalysis of study according to IQWiG methods are neccessary
- Resources are required

Pfizer