

Dose Finding in Clinical Development of 60 FDA-approved Drugs Compared to the *Learning versus Confirming* paradigm

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Objectives

- To investigate the clinical development paths, dose-ranging trial design, and dose-exposure-response characterization, which formed the basis for label dose identification in drug development programs.
- To compare these to the concepts described in Lewis B. Sheiner's *Learning versus Confirming* paradigm.

Conclusions

In many cases, confirmatory development leans more towards *learning* than *confirming* as multiple doses are commonly included in this stage, questioning sponsors' certainty of drug benefit/risk when initiating confirmatory development.

Learning in dose-ranging trials may often be limited due to the low number of included doses and narrow dose ranges, presumably affecting the extent to which model-based analysis can be meaningfully applied.

Dose-exposure-response appears to be robustly assessed in only a minority of clinical development programs, suggesting there may be room left for optimizing the benefit-risk profile of confirmatory/marketed dose(s).

Background

The highest prevailing reason for non-approval of new molecular entity applications by the US Food and Drug Administration (FDA) between 2000 and 2012 was uncertainty regarding the adequacy of proposed marketing dose(s) [1]. Furthermore, post-marketing changes to the label dosage have occurred in 21% and 18.2% of FDA-approved drugs in the period of 1980 to 1999 [2] and 2000 to 2014 [3], respectively. Recent focus on dose finding and model-informed drug development [4,5] has reiterated the importance of *Learning versus Confirming* [6] (Figure 1). We set out to investigate to which extent the *Learning versus Confirming* paradigm is integrated into drug development practice, given that the need for efficient drug development may move focus away from exploratory studies in order to initiate confirmatory studies sooner.

	Phase I	Phase IIa	Phase IIb	Phase III
Objective	Safety	Proof-of-concept	Dose response	Large-scale Efficacy/Safety
Learning/confirming	Learning	Confirming	Learning	Confirming
Number of doses	"Many"	"Few"	"Many"	"Few"
Analysis method	Estimation	Testing	Estimation	Testing

Figure 1: Clinical drug development as described by Sheiner [6], consisting of two Learn-Confirm sequences. Each clinical stage has a specific objective, resulting in the need for a differing number of doses and analysis methods.

Methods

- All information available in individual FDA approval packages on the Drugs@FDA website [7] was used to identify clinical trials relevant to dose finding and dose-exposure-response characterization.
- Clinical development programs were categorized based on initiation in healthy volunteers (IIHV) or in patients (IIP).
- Phase 1 trials were classified as *exploratory* and Phase 3 trials as *confirmatory*. Phase 2 trials were classified as exploratory except if the target indication was in oncology or if no phase 3 trials were conducted.
- Dose-ranging trials were identified using information in approval packages, namely trial description, trial objectives, FDA comments, or if mentioned in the context of label dose justification.
- Investigational drug doses in individual programs were normalized to a common administration frequency (termed active regimen normalized [active_{RN}] doses).
- The number of active_{RN} doses in each clinical development stage was summarized, distinguishing between *exploratory* first-in-patient (FIP) trials and *exploratory* post-FIP trial(s).

References

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Data Inclusion

60 drug indications approved by the FDA between February 2015 and February 2017 were included for review (Figure 2).

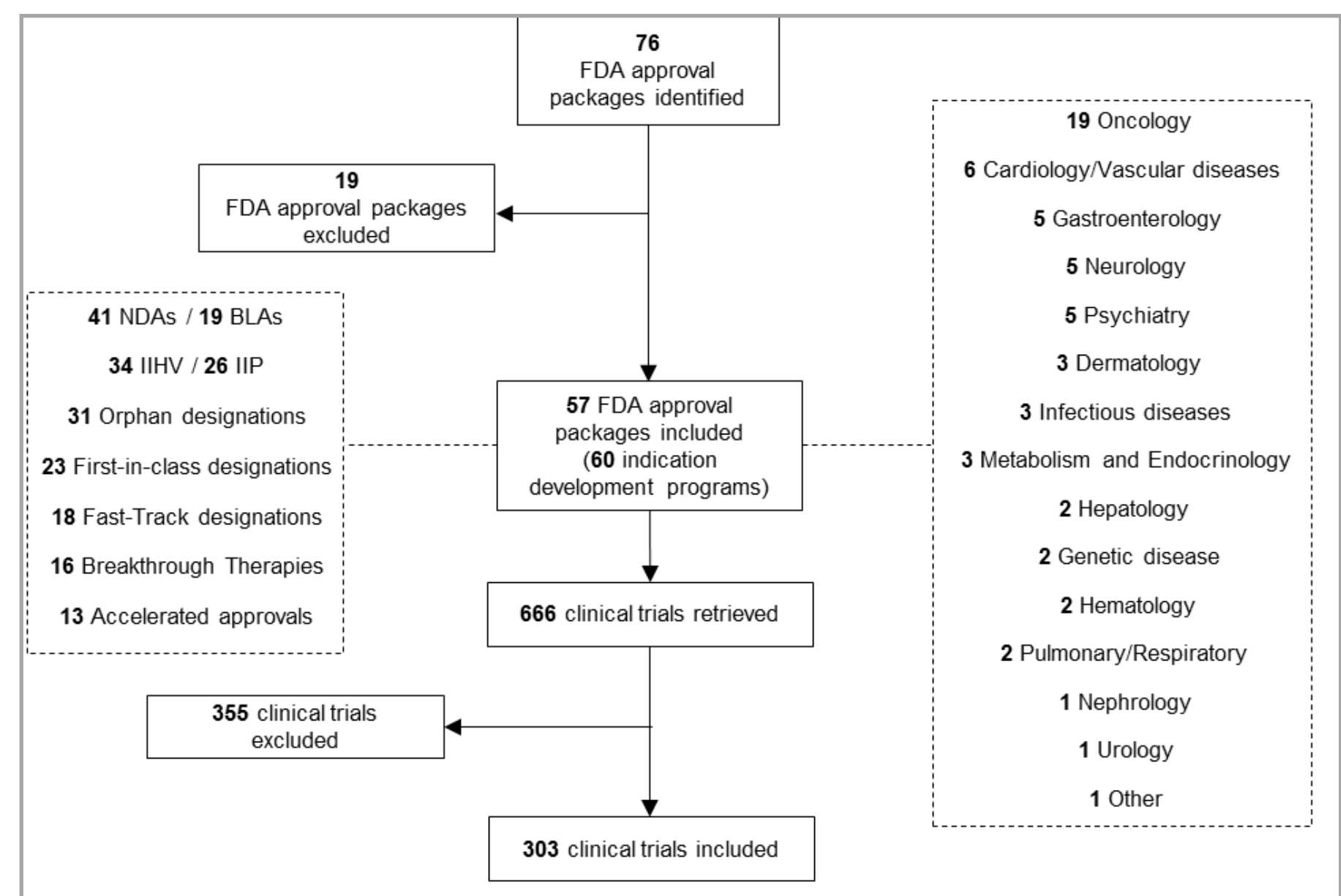


Figure 2: Flow chart showing the number of screened FDA approval packages, the number of included and excluded drugs, respectively, as well as their therapeutic area and FDA approval designation.

Clinical Development Paths

The clinical development paths in the included programs are illustrated in Figure 3.

Based on 56 development programs:

- 89% included several doses in the FIP trial
- 43% proceeded directly from the FIP trial to confirmatory trials
- 52% included multiple doses in confirmatory development
- The number of doses in exploratory development was higher for development programs with a single dose in confirmatory development compared to programs with multiple doses (median 6 vs. 4, $p = 0.004$)
- The median ratio of number of doses in *exploratory* to *confirmatory* development was 2:1 for programs IIVH and 5:1 for programs IIP

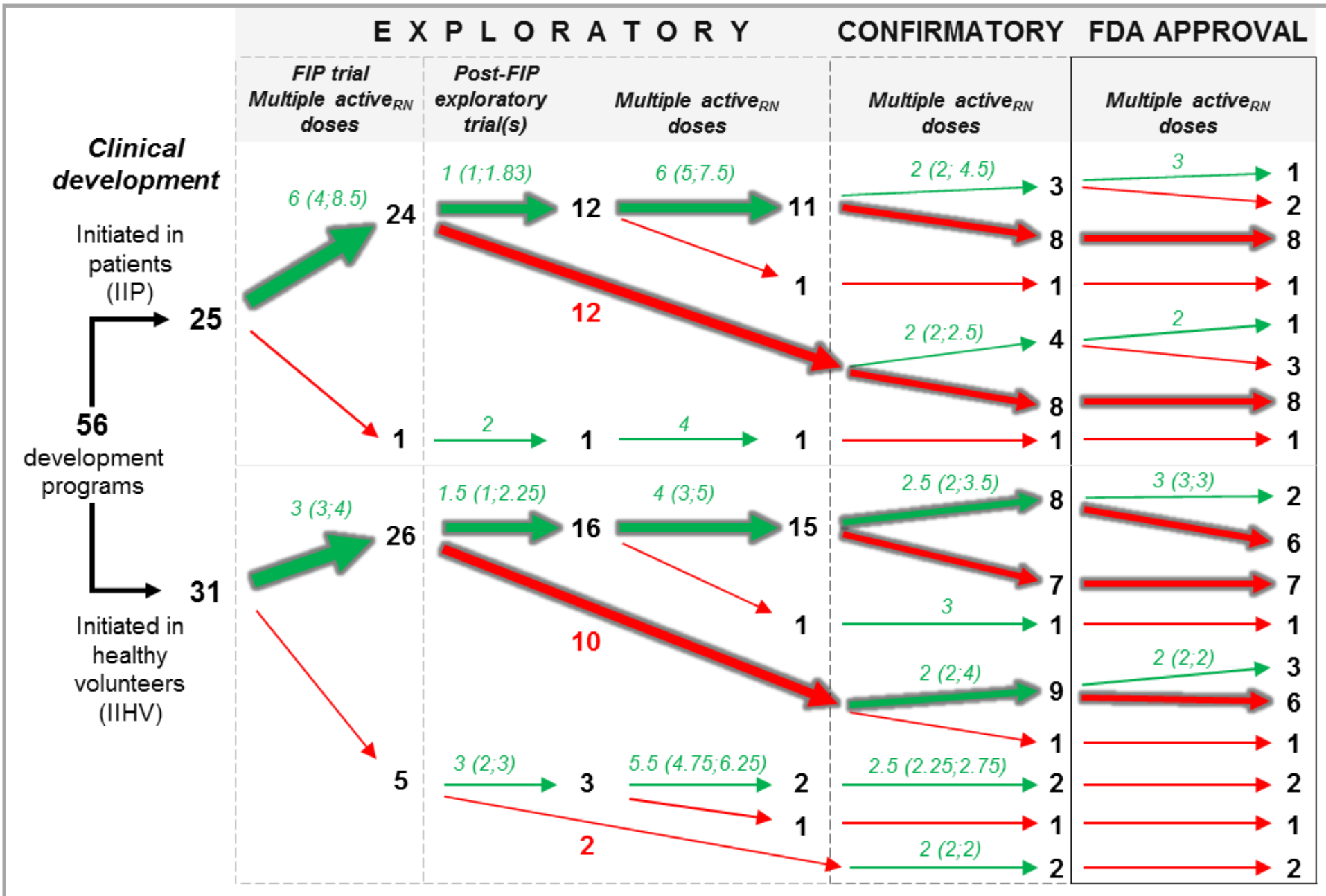


Figure 3: Clinical development paths of 56 development programs. Green arrows indicate "yes" while red arrows indicate "no". Above each green arrow the median number of active_{RN} doses is shown along with interquartile range in parentheses. FIP: first-in-patient, active_{RN}: active regimen normalized.

Dose-Ranging Trials

In 46 *exploratory* dose-ranging trials that did not implement dose-escalation:

- Only 20% included at least four investigational drug doses over an at least 10-fold dose range (Figure 4, left), as suggested at the Dose Finding Workshop hosted by the European Medicines Agency [4]
- No predominant dose spacing/allocation designs could be discerned (Figure 4, right)

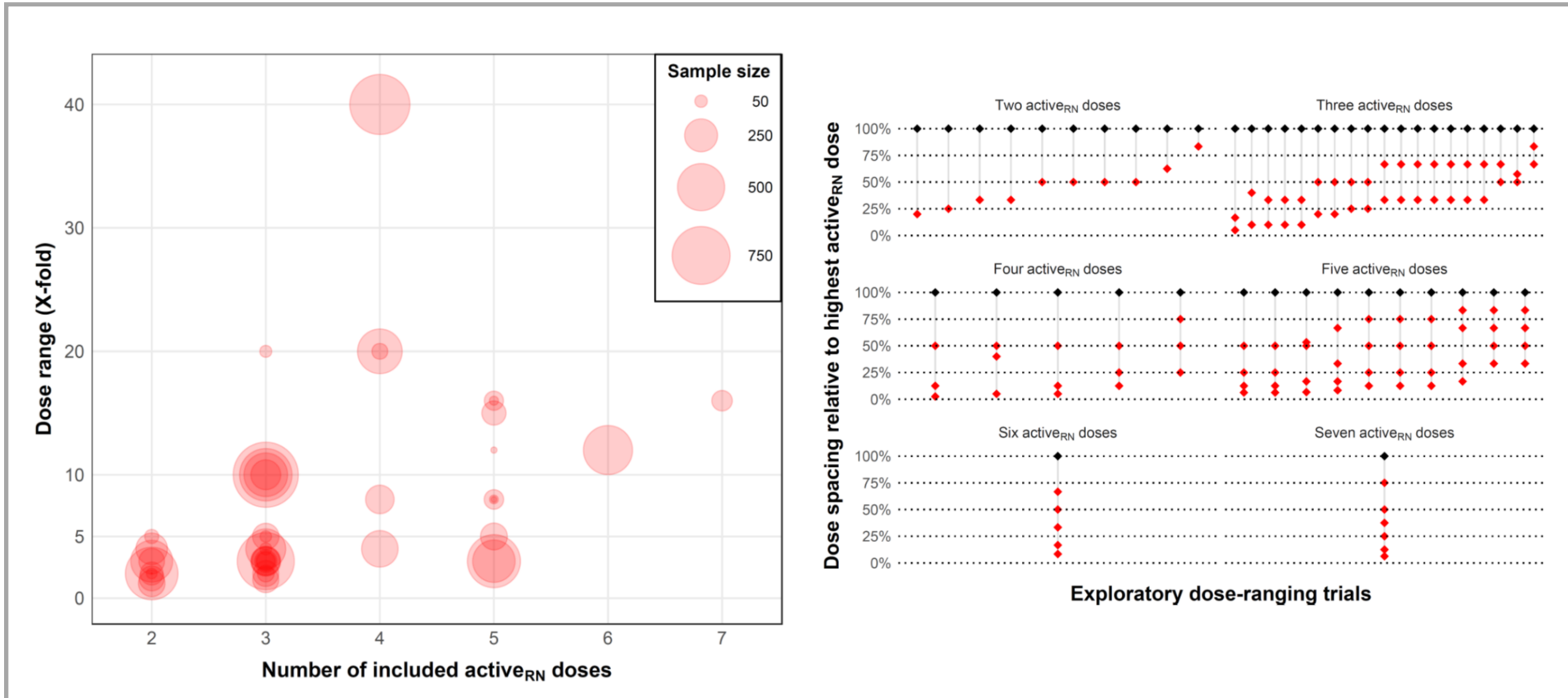


Figure 4, left: Dose-ranging trial design in terms of number of investigational drug doses, dose range, and sample size.

Figure 4, right: Dose spacing in dose-ranging trials, where the black square is the reference (highest) dose. active_{RN}: active regimen normalized

Dose-Exposure-Response

- Dose-response or exposure-response evaluation was not described in 33% of FDA approval packages
- Model-based dose-exposure-response analysis was
 - Alluded to in two of 57 approval packages
 - Described in 33 publications, of which 27 were based on *confirmatory* or pooled data.
 - Unlikely to have influenced decision-making during clinical development
- Statistical methods for establishing dose-response or exposure-response were commonly not specified
 - May have been assessed visually only
- Statistically significant associations were found for the identification of dose-response and exposure-response relationships for the assessment of efficacy (Table 1).
- No significant associations were found for safety relationships

Table 1: Evaluation of dose-exposure-response for efficacy in 60 development programs. * indicates a statistically significant association. active_{RN}: active regimen normalized, IQR: interquartile range.

Evaluation / Data	EXPLORATORY		CONFIRMATORY		POOLED EXPLORATORY & CONFIRMATORY	
	Relationship identified	Relationship not identified	Relationship identified	Relationship not identified	Relationship identified	Relationship not identified
Dose-Response Efficacy						
Number of development programs (%)	13 (22%)	5 (8%)	12 (20%)	5 (8%)	0	2 (3%)
Median number of active _{RN} doses (IQR)	4 (4; 10)*	3 (2; 3)*	2 (2; 2)	2 (2; 3)	-	4 (4; 4)
Median dose range (IQR)	15 (8; 32)*	4 (3; 4)*	2 (2; 9)	1.7 (1; 2)	-	4.5 (4; 5)
Exposure-Response Efficacy						
Number of development programs (%)	4 (6%)	0	14 (23%)	12 (20%)	5 (8%)	5 (8%)
Median number of active _{RN} doses (IQR)	4 (3; 5)	-	2 (1; 3)*	1 (1; 1)*	8 (6; 10)*	3 (2; 5)*
Median dose range (IQR)	7.5 (3; 34)	-	2 (1; 4)	1 (1; 2)	40 (8; 42)	3.8 (2; 10)