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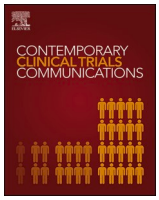

Complexity of design in early phase respiratory clinical trials; evaluating impact of primary endpoints and sponsor size

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ABSTRACT

Asthma and COPD represent most of the clinical trials in the respiratory area. The Primary Endpoint (PE) defines how trials are conducted. We hypothesised that small and mid-sized pharmaceutical companies may be innovative in the selection of their trial endpoints, to be time- and cost-effective. To test this, a record of industry-sponsored phase II trials in asthma, COPD and Asthma/COPD over 11 years was obtained. The type of PE and the influence these had on length, number of subjects and investigational trial sites were evaluated for the different disease categories.

Differences in the type of PE used by large versus small/mid-sized companies were found for both asthma and COPD trials ($p = 0.011$ and 0.025), with sponsorship influencing the conduction of these. In asthma, studies sponsored by large companies were significantly longer than those from smaller companies ($p = 0.0001$). Additionally, large companies intended to recruit more subjects (asthma: $p = 0.0048$, COPD: $p \leq 0.0001$) and use more investigational sites (asthma: $p = 1 \times 10^{-7}$, COPD: $p = 1 \times 10^{-5}$) than those from small and mid-size companies. A sub-analysis of the time and subject requirements associated with each type of PE did not provide an explanation for the differences observed.

In conclusion, this exploratory analysis indicates differences in study size, duration and type of PE used by small/mid-sized and large companies. For some types of endpoints, differences in length and study size were found. However, it wasn't possible to attribute these differences between sponsors solely to the choice of PE, pointing out to the complexity of running clinical trials.

1. Introduction

The process of drug development is typically long and competitive, such that historically, a small group of pharmaceutical companies have largely been responsible for the development of new medicines. Although big corporations still dominate the field with their larger drug development pipelines, the actual number of companies developing drugs has increased yearly since 2001 [1]. This has resulted in a spectrum of companies establishing themselves as players within the pharmaceutical industry, ranging from "spin-off" and "start-ups" to middle-sized "biotechs" and the "pharma giants," each with varying budgets, capabilities and business mentalities.

This change of paradigm within drug development is also applicable to the respiratory field, where the appearance of new companies may be accountable for the way new medicines have been clinically developed. Traditionally, the most widely used endpoint in asthma and chronic obstructive pulmonary disease (COPD) trials has been measures of lung function - in particular forced expiratory volume in 1 s (FEV_1) [2–4]. FEV_1 provides a validated measure of the airflow limitation in the lungs and is used for the diagnosis and categorisation of obstructive respiratory diseases [5,6]. However, in COPD, FEV_1 has been shown not to correlate well with symptoms, exacerbations and exercise impairment, hence not reflecting the heterogeneity of the disease [7]. Similar limitations can be observed in asthma, where FEV_1 has been used effectively

Abbreviations: LP, Large Pharmaceutical group / biotech; SP, Small to mid-sized Pharmaceutical group / biotech; COPD, Chronic Obstructive Pulmonary Disease; FDA, Food and Drug Administration; ATS/ERS, American Thoracic Society / European Respiratory Society; FEV_1, Forced Expiratory Volume in 1 s; FEF, Forced Expiratory Flow; PEF, Peak Expiratory Flow; PEFR, Peak Expiratory Flow Rate; PIF, Peak Inspiratory Flow; SGRQ, Saint George's Respiratory Questionnaire; PRO, Patient Reported Outcome; ACOS, Asthma/COPD Overlapping Syndrome.

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to evaluate the efficacy of bronchodilators, but has failed to reflect improvements in patient-centred symptoms when assessing drugs with different mechanisms of action [8]. Other frequently used and validated clinical endpoints are measures of exacerbation events. However, these are rare, and therefore, a high number of subjects and long study times have traditionally been required to explore exacerbations in asthma and COPD clinical studies.

As a result, other measures have been employed, with most of them still not approved by regulatory authorities. The lack of distinctive biomarkers for asthma and COPD has made regulators, expert groups, consortia and patient group-led efforts (FDA, the joint ATS/ERS Task Force, Innovative Medicines Initiative, COPD Biomarker Qualification Consortium …) recommend the use of multiple clinical variables to demonstrate efficacy in clinical trials. However, the use of multiple variables can be cumbersome from a patient, capability and budget perspective, adding pressure across the pharmaceutical industry, especially for 'small-to-medium-size' companies.

In the present study, we assessed whether we could observe key differences in the way 'large' and 'small-to-medium-size' pharmaceutical companies design and conduct their clinical respiratory trials. To do so, we looked across the range of primary endpoints used in recent, early phase respiratory trials and examined the potential benefits that the use of non-conventional endpoints could have in terms of trial outcomes. For this purpose, we focused on phase II trials, where more flexibility in the design is permitted as compared to studies aiming at regulatory approval and label claim (some phase III and IV trials), and where costs still allow small/medium-sized companies to carry out their studies independently.

2. Methods

2.1. Search and data management

A record of the industrial-sponsored clinical trials in asthma and COPD for the period January 2005 to January 2016 was extracted from Citeline's database Trialtrove (a database, constantly updated, covering the entire public domain using major- and over 40,000 unique information sources – i.e. trial registries, portals, PubMed), using the following search criteria: 'MeSH: Chronic Obstructive Pulmonary Disease or Asthma', 'Phase II, II/III trials', 'Start date: 1/1/2005 to 1/31/2016', 'Industry only' (which will still include industry using academic partners for example). These trials were classified into two groups, large pharmaceutical groups/biotechs (LP; >$10 billion sales) and small to mid-sized pharmaceutical groups/biotechs (SP; <$10 billion sales), based on the 2015-year sales of the company which sponsored/co-sponsored the trials. If a study had multiple co-sponsors, and those fell into the two different groups, the trial was considered to belong to the LP group (5.7% of the total cases). This approach was taken because many companies were acquired by LP and it wasn't possible to estimate the input/resources provided by the LP to the SP.

Clinical trials were subsequently classified into 4 different categories according to the type of primary endpoint used: 'lung function', 'safety/pharmacokinetics (PK)', 'exacerbations' and 'other'. The lung function category comprised those trials measuring pulmonary function via the volume and/or speed of air inhaled and exhaled. The endpoints included in this category were: FEV_1, Forced Expiratory Flow (FEF), Peak Expiratory Flow (PEF), PEF rate (PEFR) and Peak Inspiratory Flow (PIF). The safety/PK category contained those trials in which the objective was to assess the safety and/or pharmacokinetic properties of the intervention. As its name indicates, the exacerbations category included those trials assessing the efficacy of an intervention on the rate or time to an exacerbation. The category 'Other' included all those trials which did not fit in the previous categories. If a trial had more than one primary endpoint from different categories, e.g. co-primary endpoints from lung function and safety/PK, each of them were recorded. Hence, the total number of different endpoints can be higher than the actual number of trials. Those endpoints which fell into the category of 'other' were successively classified into biomarkers [inflammatory cells/nitric oxide (NO)/cytokines], exercise [6-min walking test (6MWT) and other exercise endurance tests], patient reported outcomes (PROs; test/questionnaires) and non-conventional (all the remaining endpoints) categories.

Additional data used from Trialtrove included the number of reported sites, the status of the trial, the target and actual accrual (initial and reached target of recruitment), the starting date of the trial and the date when the primary endpoints were reported. The latter ones were used to calculate the length of the trial by subtracting the starting date of the trial to the date when the primary endpoints were reported. Trials containing the same date for both the starting and reporting of the primary endpoints were excluded from the analysis of trial length (Table ST1 in the Supplementary Material). In a similar manner, 88 trials reporting 0 study sites were excluded from the analysis of this parameter. The rest of the entries were included in the analysis if available (Table ST1).

Although Trialtrove is an exhaustive collection of clinical trial data, some information has been found missing. Despite these efforts of finding the missing information to include it into our analyses, a variable amount of information for some of the parameters studied was still missing in the dataset or, as mentioned above, was deemed inconsistent (Table ST1). This lack of information was unequally distributed among groups with trials from SP consistently having less data available than those from LP. This study was performed with the assumption that the characteristics of the trials' missing data were not different from the characteristics of the data present in each category.

2.2. Statistical analysis

The aim of the statistical analysis was to explore the relationship between the variables of interest; type of primary endpoint, trial length and target accrual, across the different groups of disease and company size. A later focus was put on estimating to what extent the use of a particular type of primary endpoint influences the other variables of the trial.

Statistical analysis was performed using the R environment for statistical computing (version 3.4.1) [9]. To adhere to the normality assumption used in linear models, trial length and target accrual were transformed using the Box-Cox function and then analysed with a linear regression model (lm function). Company size (LP/SP) and disease were included as fixed effects in the linear models (with interactions when appropriate). Results were visually inspected to check deviations from the test assumptions. The residuals for target accrual deviated from normality and a permutation test (with 10,000 permutations) was used to assess significance instead of a model-based parametric test.

The number of sites could not be analysed with a linear regression model as a visual analysis of the residuals showed lack of compliance with normality and homoscedasticity. Instead, trials were divided into 6 different categories depending on the number of sites involved (1–3, 3–5, 5–12, 12–24, 24–54, +54) and the proportions of studies sponsored by LP and SP within each category were compared with a test of equal or given proportions. Cut-off values were obtained by dividing the number of sites into 6 groups based on quantiles (and were hence not chosen by the investigators). Additionally, as a sensitivity analysis, a Wilcoxon signed-rank test was used to compare the number of sites between the different categories.

The proportions of each type of endpoint and trial status among the different company size and disease categories were compared with a Fisher test.

Significance level was set at 0.05 (type I error or $\alpha = 5\%$). Charts were done with GraphPad Prism V7.0 (GraphPad Software Inc., CA, US).

Trialtrove is a collection of information on clinical trials. Had the database been complete (i.e. no missing information), thorough statistical analyses would not have been needed to assess trial characteristics.

However, as missing data is present, we used statistical analyses (under the assumptions given in the previous section) to generalize our observations also to un-observed data and to trials potentially not included in Trialtrove.

3. Results

3.1. Trial identification and characteristics

A total number of 574 clinical trials met our search criteria of industrial-sponsored clinical trials in asthma and COPD for the period January 2005 to January 2016. A subsequent analysis showed that 8 records corresponded to placeholders for trials that were never carried out and were removed from the analysis. The remaining 566 studies were classified into different categories and sub-categories as defined in the methods section (Table 1A). From those, 360 studies were sponsored by 'large pharmaceutical groups/biotechs (LP) and 206 by 'small to mid-sized pharmaceutical groups/biotechs (SP) companies, confirming that LP companies still conduct most clinical trials within the respiratory field. In the LP group, 215 trials in asthma, 141 trials in COPD and 4 trials in asthma/COPD were identified. The SP group included 132 trials in asthma, 72 trials in COPD and 2 trials in asthma/COPD. The number of trials sponsored by LP was 75% higher than SP, but the proportion of studies in asthma and COPD within both groups was comparable (60% and 39% for LP and 64% and 35% for SP, for asthma and COPD, respectively). Among all studies, 35 corresponded to combined phase II/III trials. Of those, 17 were sponsored by LP (11 in asthma and 6 in COPD) and 14 by SP (7 in asthma and 7 in COPD, unpublished observation).

3.2. Primary endpoints

We first sought to investigate the type of primary endpoints used by LP and SP in their respiratory clinical trials. In asthma studies, the statistical analysis comparing the proportion of trials in each set category showed significant differences between LP and SP (p-value = 0.011; Table 1A, Fig. 1A and Table ST2 in the Supplementary Material). LP performed 62.3% of the trials using lung function and 8.1% using exacerbations as a primary endpoint compared to 56.4% and 2.1% for SP respectively (Fig. 1A). On the other hand, the 14.3% of safety/PK endpoints in SP almost doubled those used by LP (6.7%; Fig. 1A). Both LP and SP performed a similar-although slightly higher for SP- percentage of trials using 'other' endpoints (21.5% vs 23.6%) (Fig. 1A). The type of endpoints used in COPD studies did also show statistically significant differences between LP and SP (p-value = 0.025; Table 1A and Fig. 1B). As observed for asthma, there was an increased percentage of COPD trials using lung function endpoints in trials sponsored by LP (55.6%) as compared to SP (41.6%) (Fig. 1B). On the contrary, LP performed a smaller percentage of studies using endpoints classified as 'other' (15.9% *vs* 32.5%; Fig. 1B). The percentage of trials using safety/PK and exacerbations as primary endpoint was similar among both groups (24.5% *vs* 20.8% and 3.3% *vs* 5.2%) (Fig. 1B).

The low number of trials within the category 'other' did not allow a statistical comparison between the LP and SP groups. However, in asthma, data suggested there were differences in the type of endpoints used by LP and SP (Table 1B), with LP using biomarkers as primary endpoints in 40.8% of their trials and non-conventional endpoint in 22.4%. In contrast, SP used biomarker-based endpoints for 25.7% and non-conventional endpoints for 40% of their trials. The percentage of trials using PRO endpoints was similar among the two groups (36,7% for LP and 34,3% for SP). On the contrary, in COPD, LP used less biomarkers and PRO than SP (30.8% *vs* 44% and 11.5% *vs* 28%, respectively) and more exercise and non-conventional endpoints (19.2% *vs* 8% for exercise and 38.5% *vs* 20% for non-conventional).

3.3. Trial status

To understand if the completion rate for trials sponsored by LP was different to those from SP and rule out that this factor could influence other variables analysed, the status of the studies was compared for each sponsor and disease group. No significant differences were found when comparing the proportion of trials ongoing, completed, closed or terminated between LP and SP for asthma and COPD (see Table ST3).

3.4. Trial length

We then investigated the trial length among the different categories of disease and company size (Table 2). The mean for the length of asthma studies sponsored by LP was 778 days which was statistically different as compared to the 593 days for SP-sponsored studies, with an increase of 185 days for LP ($p = 0.0001$; Fig. 2). In COPD, no statistically significant differences were found between LP and SP (670 *vs* 695 days, Fig. 2). Likewise, the length for trials sponsored by LP (426 days) was similar to those sponsored by SP (410 days) in trials investigating both asthma and COPD (Fig. 2), although in this case results were not compared statistically due to the low numbers of trials investigating both conditions. A sensitivity analysis was performed to examine whether the proportion of phase II/III trials within the LP and SP groups affected the outcome of the analysis of trial length. Excluding all trials with phase II/III status did not change the outcome, and hence the presence of such trials does not alter our conclusions.

3.5. Target accrual

Next, we examined the target accrual between the two company groups. In both asthma and COPD trials, the target accrual for LP was significantly bigger than for SP ($p = 0.0048$ and $p \leq 0.0001$ respectively; Table 3). In asthma, LP intended to recruit a mean of 224 subjects *versus* the 136 in SP trials (Fig. 3). In COPD, the mean accrual was of 200 subjects for LP and 126 for SP (Fig. 3). Studies assessing both asthma and COPD in the same trials had a target accrual of 56 subjects for LP and 115 subjects for SP (Fig. 3). As for trial length, a sensitivity analysis was performed to assess the effect of phase II/III trials on the results for target accrual. Inclusion of phase II/III trials did not change the outcome and were included in the analysis.

Table 1A
Use of primary endpoints among large and small/mid-sized pharmaceutical groups.

	Large pharmaceutical groups n = 360						Small/mid-sized pharmaceutical groups n = 206					
	Asthma		COPD		Asthma/COPD		Asthma		COPD		Asthma/COPD	
Total count	215		141		4		132		72		2	
Lung function	139	(62.3%)	84	(55.6%)	4	(100%)	79	(56.4%)	32	(41.6%)	1	(50%)
Safety/PK	15	(6.7%)	37	(24.5%)	0		20	(14.3%)	16	(20.8%)	1	(50%)
Exacerbations	18	(8.1%)	5	(3.3%)	0		3	(2.1%)	4	(5.2%)	0	
Other	48	(21.5%)	24	(15.9%)	0		33	(23.6%)	25	(32.5%)	0	
Unknown	3	(1.3%)	1	(0.7%)	0		5	(3.6%)	0	(0.0%)	0	

Abbreviations: n: number of trials; COPD: chronic obstructive pulmonary disease; PK: pharmacokinetics.

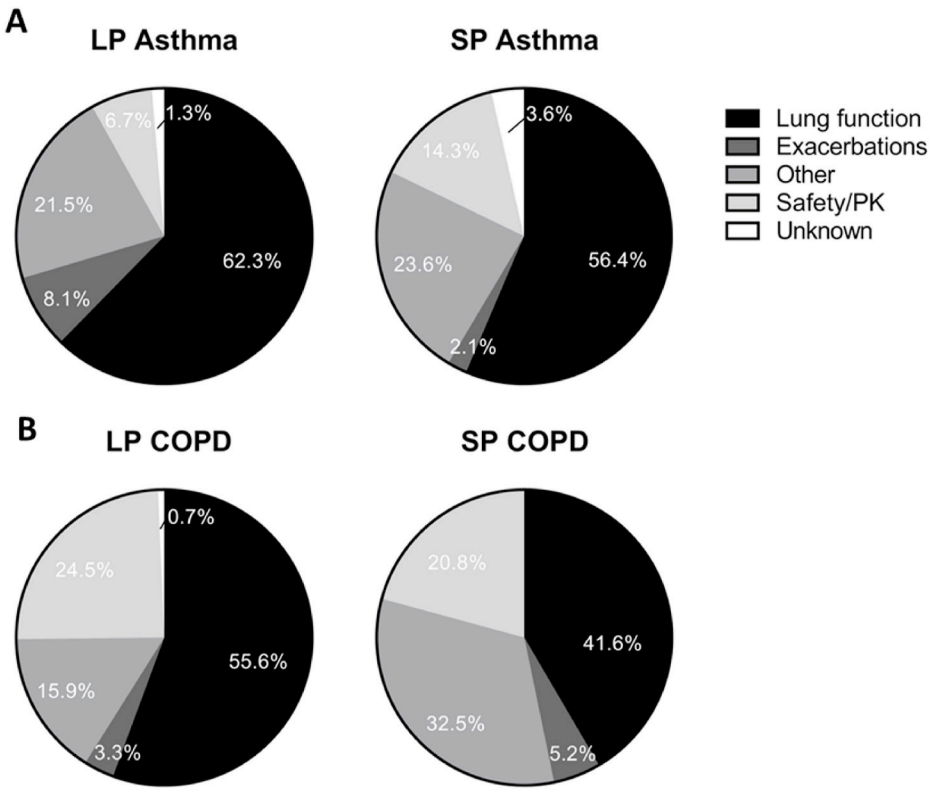

Fig. 1. Type and percentage of primary endpoints used by LP and SP in their clinical trials for Asthma (A) and COPD (B).

Table 1B
Percentage of primary endpoint subtypes among the category of others.

	Large pharmaceutical groups		Small/mid-sized pharmaceutical groups	
	Asthma	COPD	Asthma	COPD
Biomarkers	40.8%	30.8%	25.7%	44%
Non-conventional	22.4%	38.5%	40%	20%
Exercise		19.2%		8%
PRO	36,7%	11.5%	34.3%	28%

Abbreviations: COPD: chronic obstructive pulmonary disease; PRO: patient reported outcome.

Table 2
Length of trial.

Disease	Sponsor	Length (days), Mean	Length (days), Median	Length (days), SE	Length (days), SD	p-value for difference
Asthma	LP	778	715	33	456	0.0001
	SP	593	497	35	379	
COPD	LP	670	548	43	484	0.9631
	SP	695	566	65	504	
Asthma/ COPD	LP	426	331	115	230	–
	SP	410	410	41	58	

Significance was assessed using a linear regression model (lm function) and shown as the two-sided p-value. *Abbreviations*: SE: standard error; SD: standard deviation; COPD: chronic obstructive pulmonary disease; LP: large pharmaceutical group; SP: small/mid-sized pharmaceutical group.

3.6. Number of sites

We investigated the number of sites used in the selected studies, since this is known to be a parameter contributing to trial length as well as target accrual, and it may also correlate with the type of endpoint used. Studies were classified into 6 different categories, based on the reported number of sites, and the proportion of trials sponsored by LP and SP in each category was compared. Statistical analysis showed that the distribution of trials in each category was not homogenous between LP and SP ($p = 1.4 \times 10^{-8}$; Fig. 4A). Most of the studies sponsored by SP involved between 1 and 12 sites (73%), with 38% of the total requiring only 1–3 sites. On the contrary, only 43% of the trials from LP involved 12 or less sites, generally using 24–54 (21%) and +54 sites (20%; Fig. 4A).

Additionally, we compared the number of sites used in asthma and COPD studies sponsored by LP and SP. In both asthma and COPD, studies sponsored by LP required significantly more sites than SP ($p = 1 \times 10^{-7}$ and 1×10^{-5}, respectively; Table 4). The mean number of sites for asthma studies was 31, with LP using a mean of 40 and SP 16 sites (Fig. 4B). In COPD, the mean number of sites per study was 24, with LP and SP requiring 29 and 10 sites, respectively (Fig. 4B). Therefore, LP used more than 2.5-times more sites than SP. The mean number of sites for studies assessing both asthma and COPD was 7 (8 for LP and 5 for SP). Exclusion of phase II/III trials had no impact on significance and therefore were included in the analysis.

3.7. Relationship between type of endpoints, trial length and target accrual

Finally, we addressed whether there was a correlation between the type of endpoints used in a trial, the length of the trial and the number of subjects required for the trial. Of note, trials with more than one primary endpoint, in addition to trials with missing information about the primary endpoint, were not used for this analysis (38 out of 566 trials).

3.8. Length of the trials

In asthma, studies using exacerbations as primary endpoint lasted a mean of 908 days, which was significantly longer than trials using lung

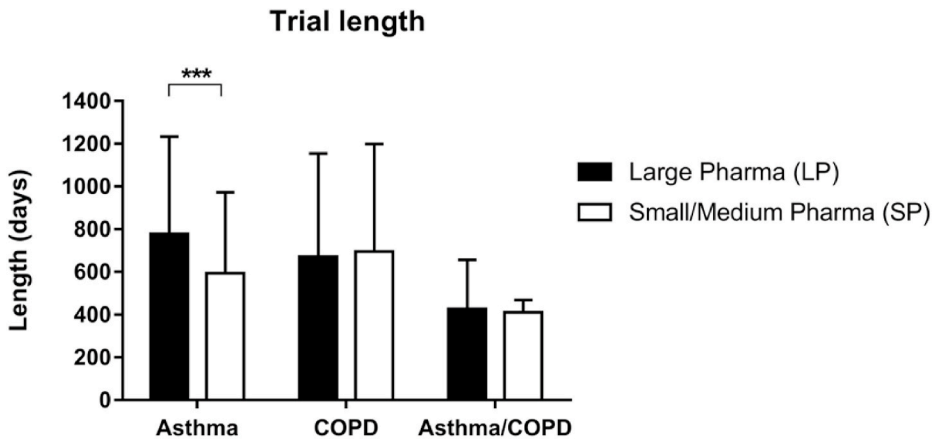

Fig. 2. Length (in days) for LP and SP trials in Asthma, COPD or Asthma/COPD. Mean ± SD. Tests performed on the least-squares means from a linear model (*p ≤ 0.05, **p ≤ 0.01 ***p ≤ 0.001).

Table 3
Target accrual.

Disease	Sponsor	Target accrual (n), Mean	Target accrual (n), Median	Target accrual (n), SE	Target accrual (n), SD	p-value for difference
Asthma	LP	224	90	21	302	0.0048
	SP	136	57	17	179	
COPD	LP	200	120	21	242	<0.0001
	SP	126	60	20	167	
Asthma/ COPD	LP	56	57	2	5	–
	SP	115	115	85	120	

A non-parametric permutation test with 10,000 permutations was used to assess significance. *Abbreviations*: n: number of subjects; SE: standard error; SD: standard deviation; COPD: chronic obstructive pulmonary disease; LP: large pharmaceutical group; SP: small/mid-sized pharmaceutical group.

function (657 days) and safety/PK (651 days) (p-values = 0.008 and 0.009, respectively; Table 5 and Table ST4A). Trials using 'other endpoints' were also significantly longer than those assessing lung function (854 *versus* 657 days; p-value = 0.01) and safety/PK (854 *versus* 651 days; p-value = 0.023 Table 5 and Table ST4A). In COPD, trials assessing exacerbations (1008 days) were longer than trials using lung function (547 days; p-value = 0.002; Table 5 and Table ST4B). No differences in the length of the studies between those using exacerbations and 'other' (906 days) or safety/PK (694 days) were found (Table 5 and Table ST4B). Additionally, those studies using 'other endpoints' and safety/PK were found to be statistically longer than those using lung function ($p < 0.0001$ and 0.011 respectively; Table 5 and Table ST4B). A sensitivity analysis showed that in COPD, the exclusion of phase II/III trials from the analysis resulted in a change of significance for the comparison between exacerbations and lung function endpoints (p-value changed from 0.0024 to 0.0654 as the mean trial length for exacerbations changed from 1008 to 844 days). No change of significance was observed for the other pair-comparisons.

Asthma studies using biomarkers as primary endpoint lasted a mean of 775 days *versus* the 999 days used for non-conventional endpoints and 809 days for trials using PRO (Table 6). In COPD, the longest trials corresponded to those studies using exercise tests as primary endpoint (1285 days), followed by studies using non-conventional (1008 days), PRO (906 days) and biomarkers (655 days; Table 6). A statistical comparison was not performed due to the low number of trials in the different groups.

3.9. Target accrual

In asthma, trials assessing exacerbations intended to recruit a mean of 366 subjects, representing a significant increase *versus* the number of subjects required for lung function- (200; p = 0.004), 'other'- (179; p = 0.0053) and safety/PK trials (124; $p < 0.0001$) (Table 7 and Table ST5A). No differences were found between trials using lung function and 'other' endpoints, but both categories showed a significantly higher target accrual than trials using safety/PK endpoints ($p < 0.0001$ and 0.0015 respectively; Table 7 and Table ST5A). In COPD, the

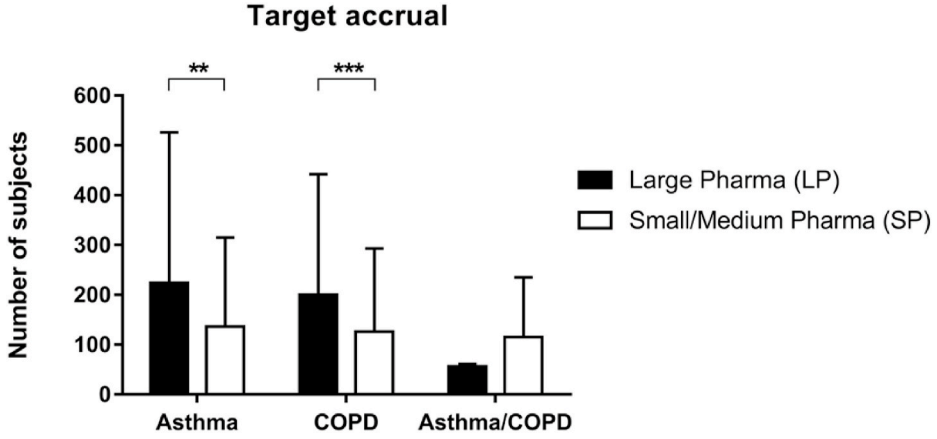

Fig. 3. Number of subjects planned to be recruited (target accrual) for LP and SP trials in Asthma, COPD or Asthma/COPD. Mean ± SD. Permutation test (*p ≤ 0.05, **p ≤ 0.01 ***p ≤ 0.001).

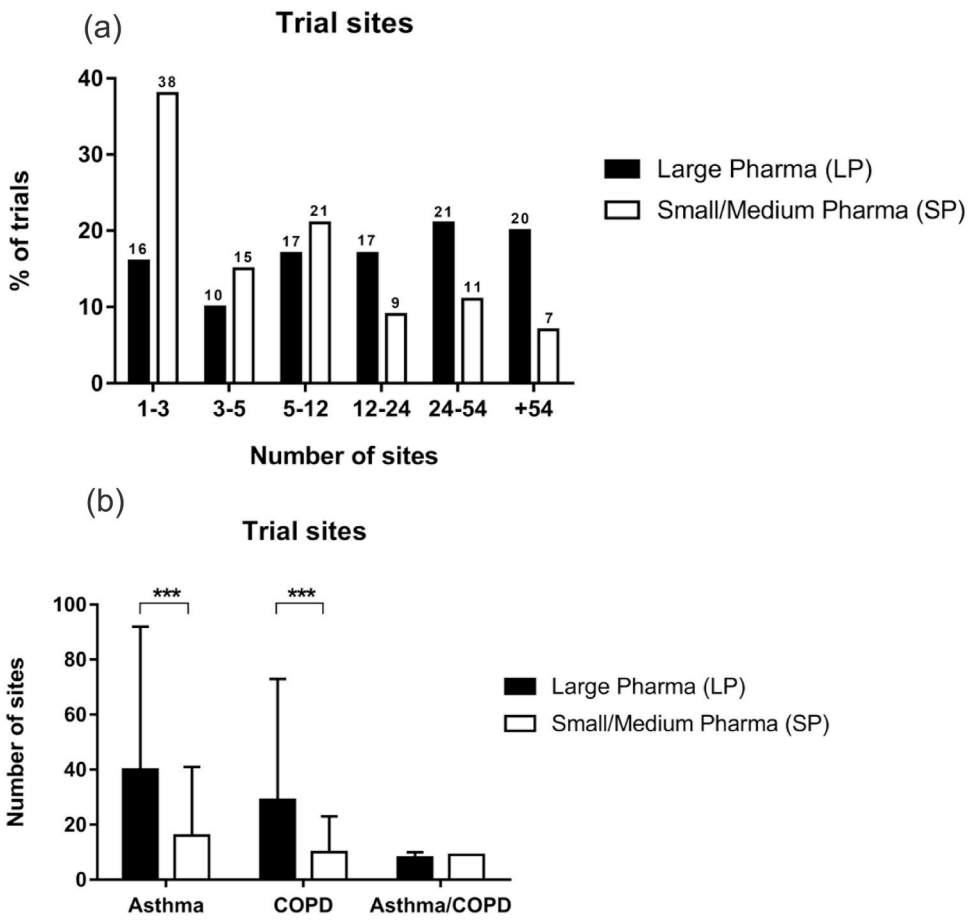

Fig. 4. Fig. 4A Percentage of trials from LP and SP according to the number of sites intended to be used in the trial. Numbers above the columns indicate the percentage for the category. Fig. 4B Number of investigational sites intended for LP and SP trials in Asthma, COPD or Asthma/COPD. Mean ± SD. Wilcoxon signed-rank test (*p ≤ 0.05, **p ≤ 0.01 ***p ≤ 0.001).

Table 4
Reported sites.

Disease	Sponsor	Reported Sites (n), Mean	Reported Sites (n), Mean	Reported Sites (n), Median	Reported Sites (n), SE	Reported Sites (n), SD	Significance (p-value)
Asthma	LP	31	40	19	4	52	1×10^{-7}
	SP		16	4	3	25	
COPD	LP	24	29	14	4	44	1×10^{-5}
	SP		10	5	2	13	
Asthma/ COPD	LP	7	8	8	1	2	–
	SP		5	5	–	–	

Significance was assessed using a test for proportions (prop.test function, data not shown) and a two-sided Wilcoxon signed-rank test. *Abbreviations*: n: number; SE: standard error; SD: standard deviation; COPD: chronic obstructive pulmonary disease; LP: large pharmaceutical group; SP: small/mid-sized pharmaceutical group.

Table 5
Trial length *versus* the type of primary endpoint.

Disease	PE type	Length (days), Mean	Length (days), Median	Length (days), SE	Length (days), SD
Asthma	Exacerbations	908	1014	80	359
	Lung Function	657	578	30	406
	Other	854	807	62	499
	Safety/PK	651	490	100	508
COPD	Exacerbations	1008	1035	171	452
	Lung Function	547	443	46	456
	Other	906	669	94	586
	Safety/PK	694	682	63	360

Abbreviations: PE: primary endpoint; SE: standard error; SD: standard deviation; PK: pharmacokinetics; COPD: chronic obstructive pulmonary disease.

Table 6
Trial length *versus* the subtype of primary endpoint among "Others".

Disease	PE type	Length (days), Mean	Length (days), Median	Length (days), SE	Length (days), SD
Asthma	Biomarkers	775	693	518	110
	Non-conventional	999	1008	628	144
	PRO	809	845	328	68
COPD	Biomarkers	655	562	421	112
	Exercise	1285	1138	622	254
	Non-conventional	1008	734	686	198
	PRO	906	669	540	204

Abbreviations: PE: primary endpoint; SE: standard error; SD: standard deviation; COPD: chronic obstructive pulmonary disease; PRO: patient reported outcome.

Table 7
Initial target *versus* the type of Primary endpoint.

Disease	PE type	Initial target (n), Mean	Initial target (n), Median	Initial target (n), SE	Initial target (n), SD
Asthma	Exacerbations	366	248	80	341
	Lung Function	200	88	19	261
	Other	179	90	25	202
	Safety/PK	124	36	79	403
COPD	Exacerbations	209	200	35	99
	Lung Function	227	132	27	270
	Other	112	60	21	134
	Safety/PK	94	60	17	109

Abbreviations: PE: primary endpoint; n: number of subjects; SE: standard error; SD: standard deviation; PK: pharmacokinetics; COPD: chronic obstructive pulmonary disease.

mean target accrual for trials using primary endpoints based on exacerbations was 209 subjects, 227 for lung function, 112 for 'other' and 94 subjects for safety/PK endpoints (Table 7 and Table ST5B). Trials using exacerbations as primary endpoint aim to recruit significantly more subjects than those using "other" and safety/PK ($p = 0.0154$ and 0.0098 respectively) but showed no difference with lung function. Lung function endpoints showed higher target accrual than "other" and safety/PK ($p = 0.0006$ and 0.0015 respectively). No significant differences in the target accrual were found between "other" and safety/PK endpoints (Table 7 and Table ST5B). Exclusion of phase II/III trials had no impact on significance and were included in the analysis.

The mean accrual for asthma studies with biomarkers as primary endpoint was 46 subjects, 276 for those studies using non-conventional and 240 for those using PRO endpoints (Table 8). Mean target accrual for clinical trials in COPD using biomarkers was 65 subjects, 144 for exercise tests, 140 for non-conventional and 134 for PRO (Table 8).

4. Discussion

Clinical trials are essential to assess the safety and efficacy of new medicines. To fulfil this aim, a series of endpoints related to the pathogenesis of disease are evaluated during the trial. One of the consequences of the use of multiple endpoints, is the increasing complexity of clinical trials in most therapeutic areas, with the number of procedures per trial protocol increasing by 57% from 105.9 in the period 2000-03 to 166.6 in 2008-11 [10,11]. Increased complexity is also associated with larger treatment periods, site "work burden" and Case Report Forms [10,11], which are partially responsible of the increasing cost of developing a drug [12,13]. Small and medium-size companies (SP) presumably have smaller budgets and capabilities as compared to large companies (LP), but still manage to carry their studies effectively and be responsible for 53% of the drugs in clinical development [14].

Table 8
Initial target *versus* the subtype of primary endpoint (those within the category of "Others").

Disease	PE type	Initial target (n), Mean	Initial target (n), Median	Initial target (n), SE	Initial target (n), SD
Asthma	Biomarkers	46	40	6	28
	Non-conventional	276	199	72	288
	PRO	240	214	33	166
COPD	Biomarkers	65	40	19	73
	Exercise	144	40	107	261
	Non-conventional	140	105	30	113
	PRO	134	100	53	129

Abbreviations: PE: primary endpoint; n: number of subjects; SE: standard error; SD: standard deviation; COPD: chronic obstructive pulmonary disease; PRO: patient reported outcome.

This study was performed under the assumption that Trialtrove database covered all the trials performed in the field and the information contained in it was accurate and updated. With regards to missing information, there was proportionally more information missing for trials sponsored by SP than for LP. This missing information was however not likely to have an impact in our analyses for the primary endpoint, where it represented less than 2.5% of the data, or limited for trial length and accrual. Although the percentages were higher, those were similar between LP and SP. Only for the comparison of the number of investigational sites, missing data for SP studies represented a significant percentage of the studies within the category and compared to LP. In this regard, whether the differences found between LP and SP could be a consequence of the different proportion of missing data (13%) was deemed unlikely, although it could not be completely ruled out. Also, trials with co-primary endpoints were included although those were not used for calculating the length, number of patients and sites. Additionally, the length of the trial was calculated by subtracting the starting date of the trial and the date when the primary endpoints were reported. We acknowledge that this method has limitations as a delay in reporting the results for reasons other than the trial conduction, would incorrectly be reflected as an increase in the trial length.

Our study confirmed what has been previously observed in the recent years. There is a high number of small-sized companies developing drugs [14], which in the case of asthma and COPD was reflected by the fact that 36% of the total number of phase II trials were sponsored by SP. Additionally, a considerable number of trials were performed in asthma as compared to COPD or asthma/COPD overlapping syndrome (ACOS), perhaps reflecting the difficulty to find new targets in these latter two diseases but also to find clinically relevant endpoints reflecting treatment effect from new modalities (other than the conventional corticosteroids/bronchodilators). The development of large molecules for the treatment of asthma *vs* COPD is also likely to have contributed to the larger proportion of trials being performed within the asthma population.

The fact that lung function measures in particular FEV_1 - were found to be the most common type of endpoints used in both asthma and COPD clinical trials, and that FEV_1 is used more in asthma than in COPD trials, was no surprise. In addition to the aforementioned reasons, changes in FEV_1 are directly related with the mechanism of action of many drugs developed for asthma during this period such as bronchodilators and therefore a good efficacy endpoint. Additionally, our analysis showed that trials using lung function endpoints were the shortest trials assessing efficacy for both asthma and COPD. These properties in combination with extensive validation and regulatory acceptance makes lung function endpoints very appealing if related to the mechanism of action of the drug.

When it comes to exacerbations, the other established endpoint, we saw a relatively modest use being higher in asthma studies from LP. Trials using exacerbations as primary endpoint had the highest requirements of patients and time in almost all the studies. It is known that asthma and COPD trials using exacerbations as primary endpoints, are lengthy and require a high number of subjects because exacerbation events are rare. And that is why exacerbations are conventionally evaluated later in phase III. Including measures of exacerbations as endpoints in phase II might explain the fact the mean trial length is increased in asthma trials sponsored by LP and that those studies require more subjects. In COPD, where the use of lung function endpoints in trials is smaller and where there may be less "choices for other endpoints", the percentage between LP and SP is more similar, with SP carrying out more studies on exacerbations. Enrichment strategies, such as seasonal recruitment and selection of subjects with frequent exacerbations are approaches that have been used to try to reduce the number of subjects and trial duration in these type of studies [15].

The small number of trials within the categories "other", did not

allow a statistical analysis and had to be analysed together, limiting the information that could be extracted from this category. Despite this limitation, we showed that a proportion of recent trials have been conducted using alternative efficacy endpoints. Biomarkers, although there's still a limitation in the number of validated ones, and patient reported outcomes (PRO), are two methodologies that have the potential to reduce the logistic and economic burden of trial conduction in respiratory diseases.

In conclusion, our exploratory analysis indicates that the choice in endpoints used by small/mid-size and large pharmaceutical companies heavily relies on established endpoints, and that these do not solely account for the differences observed in study size and duration for example. It is very likely that the influence of the primary endpoint goes beyond the size and length of the trial and assessment of other aspects such as the cost of the analysis was outside the scope of this study. This work also stresses the need for novel endpoints. Whilst the development and validation of novel endpoints can be a long process and requires a tremendous contribution from different experts and includes a long path to regulatory approval, they signify an innovation in respiratory trials and may better predict outcomes for patients.

Declaration of competing interest

All authors are or were employed by AstraZeneca during the preparation of this manuscript.

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