

# CARE: An Observational Study of Adherence to Home Nebulizer Therapy Among Children with Asthma

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## Research

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# Abstract

## Background

The prevalence of pediatric asthma in China is approximately 3%, and asthma remains poorly controlled in many of these patients. This study assessed the rate of adherence to home nebulizer treatment in pediatric patients in China.

## Methods

The CARE study was a 12-week, multicentre, prospective, observational study across 12 tertiary hospitals in China. Patients were aged 0–14 years, clinically diagnosed with asthma and prescribed home nebulizer inhaled corticosteroid (ICS) therapy for <sup>3</sup> 3 months. The primary endpoint was electronically monitored treatment adherence. Patients attended onsite visits at 0, 4, 8 and 12 weeks to assess asthma control, severity and treatment adherence (recorded by electronic monitoring devices and caregivers).

## Results

The full analysis set included 510 patients. Median treatment adherence reported by electronic monitoring devices was 69.9%, and median caregiver-reported adherence was 77.9%. The proportion of patients with well-controlled asthma increased from 12.0% at baseline to 77.5% at Visit 4. Increased time between asthma diagnosis and study enrolment was a significant predictor for better adherence (coefficient: 0.01 [p = 0.0138, 95% confidence interval: 0.00, 0.01]) and asthma control (odds ratio = 1.001, p = 0.0498, 95% CI: 1.000, 1.002). Negative attitude to treatment by the caregiver was associated with poorer asthma control.

## Conclusions

Adherence to home nebulization, a widely-used treatment for asthma, was high among Chinese pediatric patients. Asthma control improved with increasing treatment duration. These results suggest that home nebulization of ICS is an effective and recommendable long-term treatment for pediatric patients with asthma.

## Trial registration

ClinicalTrials.gov, NCT03156998.

## Background

In China, the prevalence of pediatric asthma has increased over the past 20 years and is now approximately 3% [1, 2]. The long-term goals of asthma management according to the Global Initiative for Asthma (GINA) 2016 update are to achieve good control of symptoms and maintain normal activity levels, and to minimize future risk of exacerbations, fixed airflow limitation and side-effects [3]. For

optimal control of chronic diseases such as asthma, long-term adherence to treatment is required. The GINA 2016 guidelines recommend that in all patients (including children) with persisting symptoms and/or exacerbations despite 2–3 months of controller treatment, assessment of any problems, including poor adherence, should be performed before considering a step-up in treatment [3].

There are several methods of collecting treatment adherence information from patients, but commonly this information is obtained from patient/caregiver treatment diaries. However, children and adolescents with asthma have been found to overestimate their level of adherence [4–6]. The gold standard method for measuring treatment adherence is an electronic monitoring device that digitally records the frequency of treatment administration [7, 8].

Real-world data on adherence to asthma medication in the pediatric population in China are limited. There are currently no published real-world data on adherence to home nebulization of inhaled corticosteroid (ICS) treatment in Chinese asthmatic children monitored by electronic devices or on the difference between adherence measured by electronic monitoring devices and that reported by caregivers. This multicentre, prospective, observational study aimed to assess treatment adherence in pediatric patients diagnosed with asthma and prescribed home nebulizer therapy.

## Methods

### Study design

The CARE study (NCT03156998) was a multicentre, prospective, observational study across 12 tertiary hospitals in China. Subjects were consecutively enrolled and asthma medication was prescribed as per routine clinical practice. A portable nebulizer device, POCKET AIR® MBPN002 (Microbase Technology Corp, Taiwan), for home use was supplied by the investigators for the study duration. An electronic chip was embedded into the device to record duration and frequency of nebulizer use. Subjects were informed about the purpose, procedures, risk and benefits of the study. Treatment adherence was recorded by the electronic chip, and patients/caregivers were asked to accurately record symptoms and medication use everyday using a diary card. Any incomplete or missing records were checked with the patients and completed to the extent possible during clinic visits.

The primary endpoint was electronically monitored treatment adherence, derived by dividing the actual treatment frequency by the prescribed frequency. One eligible use was defined as the use of nebulizer therapy for at least 5 minutes (cumulative) in a 30-minute period; if the prescription was twice a day, the interval between two eligible uses needed to be > 4 hours. Data were downloaded from the electronic monitoring devices at every onsite visit. The secondary endpoints were to find out:

- Treatment adherence reported by caregivers, derived by dividing the actual dose (recorded in diary) by the prescribed dose

- Proportion of patients in different treatment adherence levels, reported by electronic monitoring devices and caregivers
- Asthma severity and control status according to GINA 2016 [3]
- Factors associated with treatment adherence and asthma control

## **Ethical statement and clinical trial registration**

The study has been approved by the ethics committees of participating study centres. Signed and dated consent was obtained from patients, patients' parents, or guardians for all participants. The study was performed in accordance with the Declaration of Helsinki, International Conference on Harmonization, Good Clinical Practice and Good Publication Practice guidelines, and the applicable legislation on non-interventional studies and observational studies.

ClinicalTrials.gov, NCT03156998. Registered 16 May 2017,  
<https://clinicaltrials.gov/ct2/show/NCT03156998>

## **Patients**

Patients aged 0–14 years were eligible for study enrolment if they were clinically diagnosed with asthma according to Chinese pediatric asthma diagnosis and treatment guidelines [2, 9] and prescribed home nebulizer ICS therapy for  $\geq 3$  months. Only those with a definitive diagnosis of asthma, according to the specified guidelines, were included. Patients were ineligible for enrolment if they had an allergy to ICS, presented with other diseases/conditions that may have interfered with the study results as judged by the investigator, were participating in another ongoing clinical study, or had a parent/caregiver that was not proficient in expressing, understanding, writing and reading in Chinese (judged by the investigator).

## **Assessments**

The study comprised four onsite visits at 0, 4, 8 and 12 weeks. At Visit 1 (baseline), informed consent and medical history were obtained, GINA 2016 asthma control status [3] and lung function were assessed, and caregivers' knowledge of asthma was collected by questionnaire (Supplementary Material: Paediatric asthma knowledge questionnaire of parents). At Visits 2–4, GINA 2016 asthma control status [3], and exacerbation and treatment adherence information were collected. Lung function data were collected at each visit if tests were performed as per clinical practice. Asthma severity was assessed at Visit 1 and Visit 4, according to GINA 2016: mild asthma is asthma that can be well controlled with Step 1 or Step 2 treatment (i.e. with as-needed reliever medication alone, or with low-intensity controller treatment such as low dose ICS, leukotriene receptor antagonist or chromones); moderate asthma is asthma that can be well controlled with Step 3 treatment (e.g. low dose ICS/LABA); severe asthma is asthma that requires a Step 4 or 5 treatment (e.g. high-dose ICS/LABA) to maintain symptom control. Daily and on-demand medications were recorded in an asthma diary by the caregiver.

# Statistical analysis

The statistical analysis was primarily descriptive in nature based on the full analysis set (FAS). The FAS included all enrolled patients who fulfilled the inclusion/exclusion criteria. Sensitivity analyses were performed based on the per protocol set (PPS), which included patients having received the treatment and no major protocol deviations with baseline data and at least one post-baseline record available. Patients who withdrew informed consent during the study still met inclusion criteria for both FAS and PPS, as per protocols, and were included in both FAS and PPS analyses. Factors influencing adherence to medication and asthma control status (e.g. patients'/caregivers' attitude towards asthma medication, asthma control status, level of education, comorbidity, severity and duration of asthma, and age) were analysed using univariate and multivariate regression analyses (a stepwise algorithm for variable inclusion was performed; variables with a p-value  $\leq 0.15$  were subsequently included in a multivariate analysis).

## Sample Size

Previous studies have reported a median treatment adherence of 87% with an interquartile range of 70–94% for preschool children [10]; based on an assumption of normal distribution and a drop-out rate of 20%, a sample size of approximately 500 patients will provide a 95% confidence level with the width of  $\pm 1.8\%$ .

## Results

### Patients

Of 512 enrolled patients, 510 were included in the FAS. Overall, 381 patients completed the study (Fig. 1). Patient characteristics are given in Table 1.

Table 1  
Patient characteristics

	<b>N = 510</b>
Age (years), mean ( $\pm$ SD)	3.53 ( $\pm$ 2.42)
Age, n (%)	
< 0 years to $\leq$ 5 years	397 (78.0)
< 5 years to $\leq$ 12 years	108 (21.2)
> 12 years	4 (0.8)
Sex, n (%)	
Male	343 (67.4)
Female	166 (32.6)
Asthma severity, n (%)	
Mild	300 (59.1)
Moderate	173 (34.1)
Severe	35 (6.9)
Family history of asthma, n (%)	
Yes	65 (12.8)
No	444 (87.2)
Living environment, n (%)	
Rural	144 (28.3)
Urban	365 (71.7)
Home nebulizer therapy within 1 year before enrolled, n (%)	
Yes	235 (46.3)
No	273 (53.7)
Allergy history, n (%)	
Yes	197 (38.9)
No	309 (61.1)
Number of emergency visits/hospitalizations due to asthma in the previous year, n (%)	

SD: standard deviation

	<b>N = 510</b>
$\geq 1$	216 (42.4)
$< 1$	293 (57.6)
<b>Prescribed regimen, n (%)</b>	504 (98.8)
<b>Budesonide</b>	2 (0.4)
<b>Beclomethasone</b>	4 (0.8)
<b>Budesonide and beclomethasone</b>	
<b>Prescribed dose for budesonide (mg/day)</b>	1.20 ( $\pm$ 0.57)
SD: standard deviation	

Of the 510 patients included in the FAS, 504 (98.8%) were prescribed budesonide as long-term home nebulizer ICS therapy. The prescribed dose of budesonide was  $1.20 \pm 0.57$  mg/day (or a 1:1 budesonide-equivalent dose of beclomethasone if this ICS was prescribed [11]). Prescribed ICS therapy may have differed at each visit for any given patient due to the observational nature of the study.

## Treatment Adherence

The median treatment adherence reported by electronic monitoring devices was 69.9%, lower than the median treatment adherence reported by caregivers (77.9%). Regardless of the method of reporting treatment adherence, there was a slight decrease in median adherence over the course of the study: electronically monitored treatment adherence dropped from 78.1% at Visit 2 to 72.5% at Visit 3 and 67.8% at Visit 4 (Fig. 2A).

Nonadherence, defined as not following the asthma medication prescription for more than one day in the period between visits, was reported by 39.6%, 35.5% and 40.2% of patients at Visits 2, 3 and 4, respectively. The most common reason for nonadherence was forgetting medication instructions (Supplementary Table 1).

According to the electronic monitoring devices, most patients had an overall adherence level of  $\geq 50\%$  –  $< 80\%$ , whereas caregivers judged most patients' adherence level to be  $\geq 80\%$  –  $\leq 120\%$  (Supplementary Table 2).

## Asthma Control

GINA 2016-defined asthma control improved over the course of the study. The proportion of patients with well-controlled asthma increased from 12.0% at baseline (Visit 1) to 51.4%, 67.0% and 77.5% at Visits 2, 3 and 4, respectively (Fig. 2B).

In each level of adherence (defined as < 50%,  $\geq$  50% – < 80%,  $\geq$  80% –  $\leq$  120%, > 120%) at each visit, a large proportion of patients had well-controlled asthma (Supplementary Tables 3 and 4). The relationship between asthma control and electronically reported adherence or caregiver-reported adherence was similar (Supplementary Tables 3 and 4).

## Asthma Severity

At baseline (Visit 1), 300 (59.1%), 173 (34.1%) and 35 (6.9%) patients had mild, moderate, and severe asthma, respectively. At 12 weeks (Visit 4), the proportion of patients with mild asthma had increased to 96.0%, and the proportion of patients with moderate and severe asthma had decreased to 3.8% and 0.3%, respectively (Fig. 2C).

## Factors Associated With Treatment Adherence

Caregivers' attitudes to treatment, age, comorbidity, household income, and length of time between asthma diagnosis and study enrolment reached significance ( $p < 0.15$ ) in a stepwise variable selection procedure and were included in a multivariate analysis (see Supplementary Table 5 for all variables included in the univariate analysis).

A multivariate linear regression analysis showed that increased time between asthma diagnosis and study enrolment was a significant predictor of increased adherence to asthma medication (coefficient: 0.01;  $p = 0.0138$ , 95% confidence interval [CI]: 0.00, 0.01; Table 2).

Table 2

Analysis of factors associated with treatment adherence (electronic monitoring) using multivariate linear regression model

Variable	Category	Coefficient (95% CI)	p value
<b>Length of time between asthma diagnosis and study enrolment</b>		0.01 (0.00, 0.01)	0.0138
<b>Insurance status</b>	Urban residents' basic medical insurance	5.41 (-3.15,13.98)	0.2150
	New rural co-operative medical system	6.09 (-2.87,15.06)	0.1824
	Commercial medical insurance	4.09 (-9.62,17.81)	0.5577
	Other medical insurance	-12.91 (-32.25,6.43)	0.1902
	No medical insurance	0	
<b>Caregivers' attitudes on asthma medication</b>			
<b>I sometimes worry about diminishing effectiveness of the medication over time</b>	Strongly agree	7.75 (-19.22,34.72)	0.5727
	Agree	8.45 (-18.21,35.11)	0.5338
	Neutral	1.97 (-25.22,29.17)	0.8866
	Disagree	5.52 (-22.44,33.49)	0.6982
	Strongly disagree	0	
	No medical insurance	0	
<b>Caregivers' knowledge of asthma</b>			
<b>Can asthma be life threatening?</b>	Yes	2.04 (-4.26,8.35)	0.5242
	No	0	
<b>Do you think children with asthma need long-term medication?</b>	Yes, in accordance with a doctors' suggestions	-1.79 (-8.59,5.00)	0.6040
	No, there is no need for medication when a child is asymptomatic	-8.86 (-18.08,0.36)	0.0596

CI: confidence interval

Variable	Category	Coefficient (95% CI)	p value
	Do not know	0	
CI: confidence interval			

## Factors Associated With Asthma Control

While treatment adherence was a significant predictor of control status in the univariate analysis (Supplementary Table 6), it did not reach significance in the multivariate logistic regression analysis (Table 3).

Table 3

Analysis of factors associated with asthma control status using multivariate logistic regression model

Variable	Category	OR (95% CI)	p value
Treatment adherence	Yes	0.64 (0.37, 1.13)	0.1241
	No	1	
Length of time between asthma diagnosis and study enrolment		1.00 (1.00, 1.00)	0.0466
Number of emergency room visits due to asthma in the past 12 months		1.24 (0.98, 1.58)	0.0702
Number of hospitalizations due to asthma in the past 12 months		1.19 (0.83, 1.70)	0.3430
Father's education level	Elementary school	0.81 (0.09, 7.33)	0.8521
	High school	0.53 (0.10, 2.83)	0.4577
	University degree	0.94 (0.21, 4.18)	0.9312
	Master's degree or above	1	
Mother's education level	Unschooling	0.07 (< 0.01, 6.42)	0.2515
	Elementary school	0.44 (0.05, 3.87)	0.4603
	High school	1.19 (0.22, 6.61)	0.8391
	University degree	0.81 (0.19, 3.54)	0.7819
	Master's degree or above	1	
<b>Caregivers' attitudes to asthma medication</b>			
With long-term use, medication will prevent my child's asthma from becoming worse	Strongly agree	3.34 (0.50, 22.37)	0.2139
	Agree	3.18 (0.53, 19.15)	0.2070
CI: confidence interval			

Variable	Category	OR (95% CI)	p value
	Neutral	2.34 (0.37, 14.69)	0.3650
	Disagree	1.75 (0.28, 11.16)	0.5513
	Strongly disagree	1	
<b>Medication does not help or is not necessary for long-term use</b>	Strongly agree	3.21 (0.54, 19.23)	0.2015
	Agree	1.86 (0.66, 5.19)	0.2383
	Neutral	1.67 (0.64, 4.31)	0.2919
	Disagree	3.16 (1.20, 8.29)	0.0197
	Strongly disagree	1	
<b>In the near future, it may become difficult for me to let my child take their asthma medication</b>	Strongly agree	0.09 (< 0.01, 0.92)	0.0425
	Agree	0.18 (0.02, 1.68)	0.1313
	Neutral	0.23 (0.02, 2.19)	0.2006
	Disagree	0.11 (0.01, 1.01)	0.0512
	Strongly disagree	1	
<b>Caregivers' knowledge of asthma</b>			
<b>What is asthma?</b>	Infectious disease	0.97 (0.37, 2.54)	0.9523
	Chronic inflammatory disease	1.41 (0.61, 3.25)	0.4173
	Contagious disease	> 9999.99 (< 0.01, > 9999.99)	0.9897
	Do not know	1	
CI: confidence interval			

Length of time between asthma diagnosis and study enrolment was a predictive factor for good asthma control (odds ratio [OR] = 1.00,  $p = 0.0466$ , 95% CI: 1.00, 1.00). The attitude of caregivers towards asthma medication was also a predictor for asthma control (Table 3):

- Strongly agreeing with '*In the near future, it may become difficult for me to let my child take their asthma medication*' was a significant predictor for poor asthma control (OR = 0.09,  $p = 0.0425$ , 95% CI: <0.01, 0.92)
- Disagreeing with '*Medication does not help or is not necessary for long-term use*' was a significant predictor for good asthma control (OR = 3.16,  $p = 0.0197$ , 95% CI: 1.20, 8.29)

**Sensitivity analyses** The PPS consisted of 491 patients, excluding 13 enrolled patients whose post-baseline data were missing and 8 with major protocol deviations (i.e. violating inclusion criteria or lacking prescription frequency data). Median treatment adherence reported by electronic monitoring devices and by caregivers in the PPS (69.9% [interquartile range [IQR]: 50.5, 84.8] vs 77.8% [IQR: 52.1, 91.1]) were equivalent to those in the FAS. The proportion of patients with well-controlled asthma changed from 11.6% at Visit 1 to 51.3%, 67.2%, and 77.4% at Visit 2–4, respectively, similar to the percentages in the FAS (Supplementary Table 7). Also, no evident differences in the proportions of patients with different levels of asthma severity at Visit 1 and 4 were found between the PPS and FAS (Supplementary Table 7).

## Discussion

To the best of our knowledge, this study is the first multicentre real-world study in China to record adherence to home nebulization of ICS treatment in asthmatic children using electronic monitoring devices.

In the present study, the median treatment adherence rate reported by portable home nebulizer devices was 69.9%, which compares favourably to many previous reports among children in other regions worldwide: the median electronically monitored adherence was 58.4% and 46%, respectively, in two studies in the USA [6, 12, 13], changing from 54% and 41% at Month 4 to 47% and 31.5% at Month 12 in patients with controlled and uncontrolled asthma, respectively, in a study from Brazil [14], and 49.5% in a study from The Netherlands [15]. Results of the present study also compared favourably to other studies in China investigating treatment adherence in patients with asthma (adults or children) [16–18]. Furthermore, the World Health Organization reported that mean adherence was approximately 50% based on key studies in adults and children [19]. Most of these studies reported adherence to metered-dose inhaler (MDI) [6, 12–15]; comparatively, our results suggest that a home nebulizer device may facilitate better treatment adherence in pediatric patients.

Self- or caregiver-reported adherence is another common method of recording adherence to asthma treatment. This method comes at a lower cost than monitoring adherence electronically; however, this method is subjective and can therefore lead to reporting inaccuracies (caregiver reports were previously found to be only 60% accurate) [7]. Measuring treatment adherence using electronic monitoring devices

is considered the gold standard method for accurate reporting of adherence because every use is recorded digitally [7]. We used this gold standard method alongside caregiver reports in our study and found that the rate of electronically monitored treatment adherence was lower than that reported by caregivers (77.9%). These findings support the notion that treatment adherence is often overestimated by parents/caregivers. The discrepancy between caregiver-reported adherence and actual adherence has been noted previously [6].

Uni- and multi-variate analyses showed that an increased time between diagnosis and study enrolment (i.e. a longer course of disease) was a significant predictor for increased adherence. In the study by Ma *et al.*, only 22.9% of newly diagnosed patients reported good treatment adherence, compared to 63.9% with a history of asthma demonstrating good adherence [16]. These observations may be due to patients or caregivers benefiting from having time to gain experience of the disease and its management, and this could underly the increased rate of adherence observed in our study compared with previous reports [6, 12–15].

Despite a good median treatment adherence across all patients, over the course of this 12-week study treatment adherence decreased regardless of the method of reporting. This phenomenon has been observed previously in pediatric patients with asthma [5, 6, 14, 16, 20], and may be due to patients and caregivers falling into certain behaviours that lead to a decline in treatment adherence over time. Contributors to a lack of adherence include forgetting medication instructions, insufficient caregiver education on the importance of adherence, short-term symptom relief, and concerns about side effects [16, 21], which may be improved by approaches such as using electronic monitoring devices incorporating reminder alarms [22, 23] and patient and caregiver education [16, 24, 25].

The proportion of patients with well-controlled and mild asthma increased while that with uncontrolled and severe asthma decreased over the course of the study. We reported a more rapid increase in the proportion of patients with GINA-defined controlled asthma compared to patients treated with beclomethasone dipropionate and chlorofluorocarbon via pressurised MDI (BDP-CFC-pMDI) plus albuterol pMDI for as-needed symptom relief (0%, 17.6%, 41.2% and 62.7% at baseline and Month 4, 8 and 12, respectively) [14]. Furthermore, a retrospective analysis of adult and pediatric patients with asthma (N = 8,188) prescribed ICS/LABA delivered by dry-powder inhaler or pMDI reported that at the end of the study (6 or 12 months) only 18% had GINA-defined controlled asthma [26]. Together, these studies suggest that home nebulisation of ICS therapy may facilitate a more rapid improvement in asthma control compared to other methods. The type of nebulizer used may also impact adherence and efficacy; our findings complement those of Zhou *et al.*, who demonstrated that using a 'smart' nebulizer incorporating electronic monitoring to administer ICS therapy resulted in higher adherence rates and significantly improved clinical outcomes compared to conventional nebulizer use [17].

Uni- and multi-variate analyses showed that increased time between diagnosis and study enrolment was a significant predictor of good asthma control. We also found that a negative caregiver attitude was associated with poorer asthma control, perhaps due to a reduced treatment adherence or less care being

taken when using the nebulizer. An association between treatment adherence and asthma control has been reported before [13]. However, another study showed that intermittent therapy with high-dose (1 mg twice daily) budesonide provided similar benefits to paediatric asthma patients in terms of exacerbation reduction compared with low-dose daily therapy (0.5 mg nightly) [27]. In the present study, an association between treatment adherence and asthma control was not found.

Given that the treatment adherence decreased over time, we recommend that asthma management efforts be centred around patient and caregiver education that focuses on strategies to increase adherence. A focus on the importance of adherence to ICS treatment may prove vital for patients and caregivers with less experience or less knowledge of asthma and its treatment. These concepts are supported by O'Byrne *et al.*, who suggest that poor asthma control is driven in part by insufficient use of ICS, and that the reason for this is inconsistent and sub-optimal education and advice given to the patient and/or caregiver by their physician [28].

One limitation of this study is that patients at tertiary hospitals may not be representative of the whole population of China, and the adherence of these patients may not represent the adherence of patients treated in secondary or community hospitals. In addition, the use of onsite visits and diary entries to record adherence may inadvertently lead to an increase in adherence when compared to a strategy comprising only passive methods of recording nebulizer use and less frequent onsite visits. Since patients/caregivers were aware that their adherence was going to be recorded, this may have influenced their compliance with prescriptions, leading to better adherence and patient outcomes. Moreover, the high adherence and good control of asthma observed in this study might be related to the use of nebulizers, which are simple and not prone to user errors compared with other inhalers (MDI or dry powder inhaler), and therefore the results may not be generalizable to patients using other inhaler devices.

## Conclusions

Results of this study show that the rate of adherence to home nebulizer treatment in Chinese pediatric patients is good relative to prior reports in other countries and compared to other methods of ICS delivery. Furthermore, GINA-defined asthma control improved as the duration of treatment increased. We conclude that home nebulization of ICS is an effective long-term treatment method for pediatric patients with asthma.

## Abbreviations

CI, confidence interval; COPD, chronic obstructive pulmonary disorder; FAS, full analysis set; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; OR, odds ratio; SD, standard deviation.

## Declarations

### Ethics approval and consent to participate

The study has been approved by ethic committees of participating study centres. Signed and dated consent was obtained from patients, patients' parents, or guardians for all participants. The study was performed in accordance with the Declaration of Helsinki, International Conference on Harmonization, Good Clinical Practice and Good Publication Practice guidelines, and the applicable legislation on non-interventional studies and observational studies.

### **Consent for publication**

Not applicable

### **Availability of data and materials**

The datasets generated and/or analysed during the current study are available via the AstraZeneca Group of Companies – Data Request Portal at: <https://astrazenecagroup-dt.pharmacm.com/DT/Home>

More information on AstraZeneca's clinical trials disclosure policy is available at: <http://astrazenecagrouptrials.pharmacm.com//ST/Submission/Disclosure>

### **Competing interests**

The authors declare that they have no competing interests.

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### **Author's contributions**

DZ, DC, LL, YZ, YS, CZ, LZ, JP, QC, TA, and QN contributed equally to the design of the study, drafted the initial manuscript, and reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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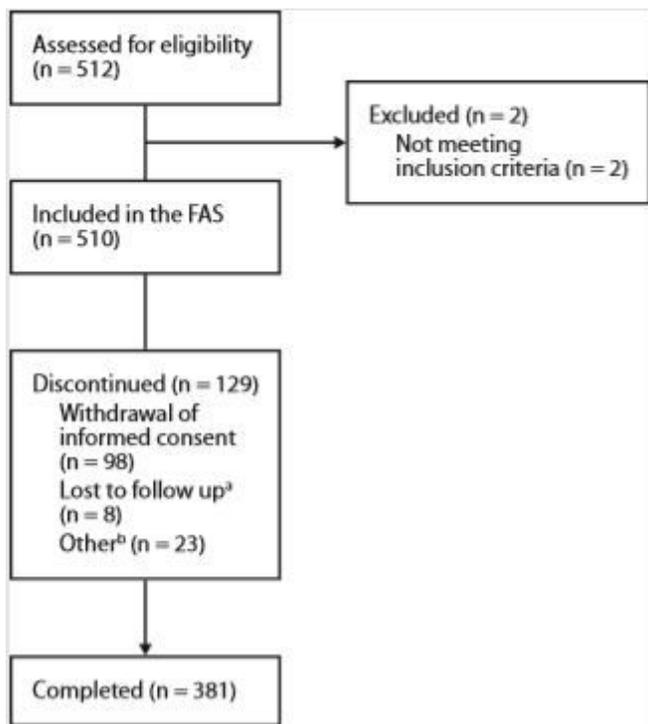
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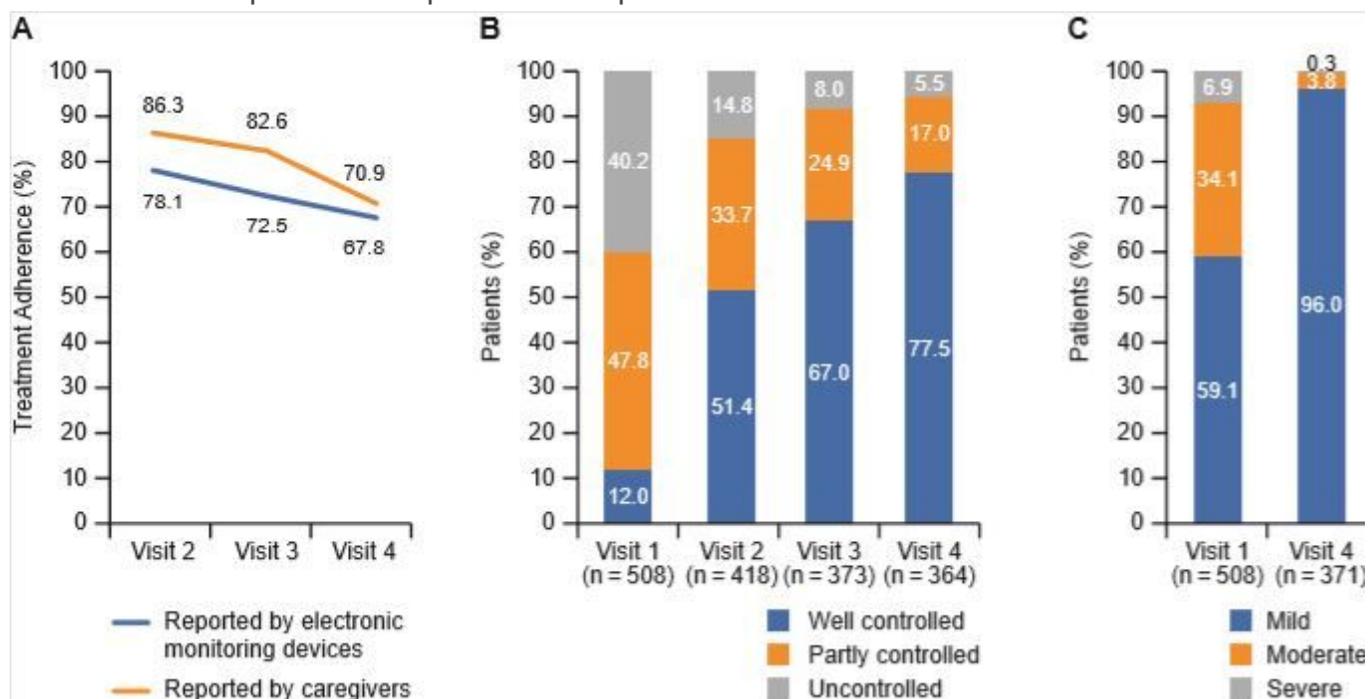
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## Figures



**Figure 1**

Patient flow a Not willing to attend hospital visit or unable to be contacted b Parent/caregiver terminated treatment due to perceived improvement in patient's condition



**Figure 2**

Changes in treatment adherence, asthma control and asthma severity over the course of the study A. Treatment adherence reported by electronic monitoring devices or by caregivers; B. Asthma control status across Visits 1–4; C. Asthma severity at Visits 1 and 4.

## Supplementary Files

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