

Journal Pre-proof

Real-world use of beclometasone dipropionate and formoterol fumarate NEXThaler® and asthma control among adult asthmatic patients in Europe: The results of the NEWTON Study

Fulvio Braido, Kai-Michael Beeh, Carolina Cisneros Serrano, Anh Tuan Dinh-Xuan, Lilla Tamási, Antígona Trofor, Eleonora Ingrassia, Alessio Piraino, Cristiano Caruso, on behalf of the NEWTON study group

PII: S0954-6111(25)00287-2

DOI: <https://doi.org/10.1016/j.rmed.2025.108224>

Reference: YRMED 108224

To appear in: *Respiratory Medicine*

Received Date: 3 April 2025

Revised Date: 18 June 2025

Accepted Date: 26 June 2025

Please cite this article as: Braido F, Beeh K-M, Serrano CC, Dinh-Xuan AT, Tamási L, Trofor A, Ingrassia E, Piraino A, Caruso C, on behalf of the NEWTON study group, Real-world use of beclometasone dipropionate and formoterol fumarate NEXThaler® and asthma control among adult asthmatic patients in Europe: The results of the NEWTON Study, *Respiratory Medicine*, <https://doi.org/10.1016/j.rmed.2025.108224>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2025 Published by Elsevier Ltd.



1 **ORIGINAL RESEARCH**

2 Braido F et al

3 **Real-world use of beclometasone dipropionate and**
4 **formoterol fumarate NEXThaler® and asthma control**
5 **among adult asthmatic patients in Europe: The results**
6 **of the NEWTON Study**

7 Fulvio Braido¹, Kai-Michael Beeh² (ORCID ID 0000-0001-9067-118X), Carolina Cisneros
8 Serrano³ (ORCID ID 0000-0003-4297-4199), Anh Tuan Dinh-Xuan⁴ (ORCID ID 0000-0001-8651-
9 5176), Lilla Tamási⁵, Antigona Trofor⁶ (ORCID ID: 0000-0003-3252-7715), Eleonora Ingrassia⁷
10 (ORCID ID 0000-0002-6597-0556), Alessio Piraino⁸ (ORCID ID 0000-0002-8029-2159), Cristiano
11 Caruso⁹ (ORCID ID 0000-0001-7631-029X) on behalf of the NEWTON study group¹⁰

12
13 ¹IRCCS Ospedale Policlinico San Martino, Università di Genova, DiMI, Genoa, Italy; ²Insaf
14 Respiratory Research Institute, Taunusstein, Germany; ³Department of Neumology, University
15 Hospital La Princesa, Madrid, Spain; ⁴Department of Respiratory and Sleep Medicine, Cochin
16 Hospital, Université Paris Cité, Paris, France; ⁵Department of Pulmonology, Semmelweis
17 University, Budapest, Hungary; ⁶“Grigore T. Popa” University of Medicine and Pharmacy, Iasi,
18 Romania – Clinic Hospital of Pulmonary Diseases, Iasi, Romania; ⁷Chiesi Italia S.p.A., Parma,
19 Italy; ⁸Chiesi Farmaceutici S.p.A., Global Medical Affairs - AIR Parma, Italy; ⁹UOSD Allergy and
20 Clinical Immunology, Fondazione Policlinico A. Gemelli, IRCCS, Catholic University of Sacre
21 Heart, Rome, Italy; ¹⁰see Collaborators.

22
23
24 Correspondence:

25 Fulvio Braido, Respiratory Diseases and Allergy Clinic, IRCCS, Ospedale Policlinico San Martino,
26 Genova, Italy, University of Genoa.
27 Email fulvio.braido@unige.it
28 ORCID ID: 0000-0003-2460-4709

Abstract

Purpose: The NEWTON study aims to describe clinical characteristics and evolution of asthma control of adult asthmatic patients treated with extrafine beclometasone dipropionate and formoterol fumarate (BDP/FF) NEXThaler® 100/6 µg.

Subjects and methods: NEWTON (NCT05168995) is a European multinational, multicentre, observational, prospective cohort study that included adults with uncontrolled or poorly controlled asthma, starting BDP/FF NEXThaler® 100/6 µg treatment within 14 days of enrolment and with no use of extrafine formulations in the previous 6 months. Improvement of asthma control, lung function, quality of life (QoL), treatment adherence, and satisfaction with the device were assessed after 3 and 6 months from the enrolment visit. In addition, safety events were monitored.

Results: 620 subjects were enrolled in the study. 423 completed the ACQ-5 questionnaire at enrolment and at least once during the following 6 months. 69.3% of patients were initiated on maintenance and reliever treatment. At baseline, the median ACQ-5 score was 2.0. After 6 months the median ACQ-5 score had decreased significantly to 0.6 ($p < 0.0001$). Similarly, after 6 months 66.1% of patients showed improved asthma control. The proportion of subjects with poorly controlled asthma fell from 65.1% to 17.5%. These improvements were consistent with the 3-month follow-up results and improved lung function, QoL, treatment adherence and device satisfaction. No new safety concerns were reported.

Conclusion: Results of the NEWTON study confirm the effectiveness and safety of the extrafine fixed combination of BDP/FF NEXThaler® 100/6 µg in adults with uncontrolled asthma in a real-world setting.

Keywords BDP/FF; NEXThaler®; asthma; extrafine; real-world

52 **Highlights:**

- 53 • NEWTON is an observational study on asthma patients in Europe.
- 54 • Patients are followed for up to 6 months from start of BDP/FF NEXThaler® 100/6 µg.
- 55 • Rapid and sustained asthma control with BDP/FF NEXThaler® 100/6 µg is found.
- 56 • Poorly controlled asthma dropped from 65.1% to 17.5% at the end of the study.
- 57 • No new safety concerns emerged during the study, confirming treatment tolerability.

Introduction

Asthma is a heterogeneous disease characterised by chronic inflammation of the airways, affecting around 300 million people worldwide, with increasing prevalence and significant costs to society and the healthcare system. [1-3] According to the Global Initiative for Asthma (GINA), the goal of asthma treatment is to achieve the best possible long-term outcome for the subject, i.e., that symptoms remain under control in the long term and that the risk of exacerbations, a deterioration in lung function and the occurrence of adverse drug effects is minimized. ^{GINA 2024} The treatment of asthma should also aim to control the disease with the minimum amount of medication over a prolonged period, taking into account the tolerability of treatment, the potential for adverse effects and the cost. [3]

In recent years, effective new pharmacological options or new combinations of existing drug therapies have become available. [4] In particular, real-world studies have shown better asthma control and better quality of life (QoL) may be achieved with extrafine beclometasone dipropionate (BDP)/formoterol fumarate (FF) compared to the fixed combinations budesonide/formoterol or fluticasone/salmeterol. [5,6] The fixed BDP/FF NEXThaler® 100/6 µg combination can be used as both maintenance and reliever treatment (MART), allowing patients to manage their asthma with a single inhaler and potentially improving adherence. [7]

Advancements in pharmaceutical research have led to the development of fixed-dose combinations of BDP/FF 100/6 µg resulting in extrafine powder formulations also available in an innovative delivery device, the NEXThaler®. The extrafine formulation improves the deposition into the peripheral airways so that a larger proportion of the inhaled compound reaches the pharmacological target in the small airways while maintaining consistent efficacy and safety. [8-

10] The NEXThaler® proved to be an effective, well-tolerated and easy-to-use delivery device for the administration of maintenance and reliever therapy drugs. [11-15]

Despite favourable results in clinical trials, there is a significant discrepancy between the GINA treatment goals and the actual level of asthma control achieved, as many patients still have poorly controlled asthma. Large-scale population studies are essential to understand asthma characteristics and treatment outcomes better. The NEWTON study, a multinational, real-world study, aimed to obtain a better understanding of asthma characteristics and to assess asthma control during treatment with BDP/FF 100/6 µg treatment using the NEXThaler® in a European patient population over a follow-up period up to 6 months.

Material and methods

Study design and participants

NEWTON (NCT05168995) is a multinational, multicentre, observational, prospective cohort study to evaluate the effects of BDP/FF 100/6 µg fixed combination administered via a DPI (NEXThaler®) in a real-world context. Details of inclusion and exclusion criteria, study treatments, study objectives have been reported previously (<https://doi.org/10.2147/JAA.S422832>). [16] The study was performed according to the Declaration of Helsinki, Good Pharmacoepidemiology Practices (GPP) and applicable regulatory requirements and was approved by the ethics committees of all participating institutions before the start of enrolment and data collection. [17] The study involved 52 respiratory medicine centres in six European countries, of which 47 enrolled at least one patient (6 sites in France, 7 in Germany, 4 in Hungary, 19 in Italy, 5 in Romania, and 6 in Spain).

The study included adult subjects with not-well-controlled or poorly controlled asthma, according to the clinical assessment, who started treatment with BDP/FF NEXThaler® 100/6 µg at enrolment or no longer than 14 days before enrolment and who had not been treated with extrafine

formulations in the 6 months before enrolment. Two study populations were defined: the Safety Analysis Set (SAF) and Full Analysis Set (FAS) (see details in Figure 1).

Endpoints

The primary endpoint was the probability of improvement in asthma control status using the ACQ-5 score, 6 months after starting treatment with BDP/FF NEXThaler® 100/6 µg. The proportion of subjects whose ACQ-5 score had improved after 6 months compared to baseline was measured.

The secondary endpoints included other BDP/FF NEXThaler® 100/6 µg treatment effectiveness measures such as asthma control, quality of life, treatment adherence, lung function, patient satisfaction with the inhaler and asthma exacerbations after 3 and 6 months.

The safety profile was also evaluated.

All adverse events starting at or after the informed consent signature were classified as treatment emergent adverse events (TEAEs) and were included in the safety analysis.

Patient-reported outcomes (PRO) assessments

In the NEWTON study, the Bring Your Own Device approach was used, i.e. each participant completed the questionnaires/structured questions using their electronic device. The ePROs were completed at baseline and at the 3-month and 6-month during on site and/or remote visits (if foreseen by the clinical practice of the site). The study used the following questionnaires:

(1) the ACQ-5 to assess asthma control,[18-20] (2) the EuroQol 5-dimension 5-level (EQ-5D-5L) to assess the health-related quality of life, [21,22] (3) the TAI-12 to assess treatment adherence and (4) a structured questionnaire consisting of three questions to assess satisfaction with the device (Figure A1). [16, 23] ACQ-5 scores were classified into three groups ('grouped scores'): well-controlled asthma (ACQ-5 score ≤ 0.75); not well-controlled nor poorly controlled asthma (ACQ-5 score 0.75–1.5), or poorly controlled asthma (ACQ-5 score ≥ 1.5). [1, 18-20] EQ-5D-5L index scores can range from less than 0 to 1, with 0 being the value of a health state equivalent to death, negative

values (<0) representing a health state worse than death, and 1 being the value of full health. [21, 22] TAI scores in the range from 10 to 45 indicate 'poor adherence', between 46 and 49 indicate "intermediate adherence", and equal to 50 indicate 'good adherence'). [23]

Statistical analyses

Continuous variables were described with the number of observations, median and interquartile range (IQR), while categorical variables were characterised by the number of subjects, percentages and 95% confidence intervals (95%CI), when applicable. Statistical tests to determine the significance of changes of primary and secondary endpoints over time and of group differences were performed at a 0.05 significance level (two-sided). The safety endpoints were analysed by counting the number of subjects (with calculated proportions) with TEAEs, TEAEs related to BDP/FF NEXThaler® 100/6 µg, serious adverse events (SAEs), SAEs related to BDP/FF NEXThaler® 100/6 µg, TEAEs leading to treatment discontinuation, TEAEs leading to death and specific special situations, if any. Missing data were not imputed, hence patients with missing data were excluded from the analyses of that variable(s), unless differently specified.

Analyses were performed using SAS Enterprise Guide v. 8.2 and SAS 9.4 (SAS Institute, Cary, NC, USA). Study design and conduct, data monitoring, eCRF set-up, and statistical analyses were performed by IQVIA Solutions Italy srl on behalf of Chiesi Italia S.p.A.

Results

Patient disposition and demographics

The study began in April 2022 (first patient, first visit) and was completed in February 2024 (last patient, last visit). The database was locked for analyses in April 2024.

A total of 620 subjects were enrolled in the study. Of those, 609 subjects started the treatment with BDP/FF NEXThaler® 100/6 µg at baseline or in the 14 days before baseline and were included in the SAF; 423 participants completed the ACQ-5 at baseline and at least once during the 6-month observation period (FAS population) (Figure 1). The median observation period (IQR) in the FAS population was 6.2 months (6.0-6.5), which was in line with expectations.

The demographic and clinical characteristics of the FAS population are shown in Table 1 and Table A1: 67.8% (n=287) of subjects were female, 74.7% (n=316) were ≥ 35 years old, 65.0% (n=275) were non-smokers and 60% (n=254) were overweight or obese. The median time since diagnosis of asthma was 8.7 (IQR: 1.8-19.9) years. 14.2% (n=60) of subjects had moderate or severe exacerbations in the previous 12 months. The median ACQ-5 score at baseline was 2.0 (IQR: 1.2-3.0). The majority (87.5%, n=370) reported not well or poorly controlled asthma. As the ACQ-5 score was not an eligibility criterion, there were also participants (12.5%, n=53) who reported a well-controlled level of asthma, according to the ACQ score.

92.0% (n=389) of subjects had been previously treated with inhaled asthma medications; among them, 74.8% (n=291) had used inhaled corticosteroids (ICS) (Table A2).

The physicians decided in favour of treatment with BDP/FF NEXThaler® 100/6 μ g micrograms primarily for reasons including poor symptom control (93.9%, n=397, physicians' statements) and for reasons including the type of device and its formulation (38.3%, n=162). 69.3% (n=293) of subjects used BDP/FF NEXThaler® 100/6 μ g as MART while 30.7% received the treatment as maintenance only (Table A3).

Improvements in asthma control (ACQ-5 score) and treatment changes at the end of observation

Among the subjects who completed ACQ-5 at baseline and 6-months (n=395), 66.1% (n=261, 95%CI: 61.2-70.7) had improved their level of asthma control. In this subset of population, the median [IQR] ACQ-5 score significantly decreased (0.6 [0.0-1.2] vs. 2.0 [1.2-3.0], $p < 0.0001$, n=395), which corresponded to a decrease of the proportion of subjects with poorly controlled asthma from 65.1% (n=257) to 17.5% (n=69). Taking together the proportion of subjects with not-well-controlled asthma and poorly controlled asthma, the proportion decreased from 87.6% (n=346) at baseline to 43.3% (n=171) at the 6-month follow-up (Figure 2A). The median [IQR] ACQ-5 score significantly decreased also at the 3-month visit in comparison to baseline (0.8 [0.2-1.4] vs 2.2 [1.2-3.0], $p < 0.0001$, n=359), which corresponded to a decrease of the proportion of subjects with poorly

controlled asthma from 67.4% (n=242) to 19.2% (n=69). Figure 2B displays the change in ACQ-5 in the subset of the FAS population with the ACQ-5 score data at all time points (n=331), which shows a significant change in asthma control after 3 and 6 months from baseline (0.8 and 0.6 at 3 months and 6 months, respectively; $p<0.0001$).

Since the study included also subjects who self-reported well-controlled asthma (according to ACQ-5), a sensitivity analysis was performed to evaluate asthma control including only the subset of the FAS population with an ACQ-5 score > 0.75 (that is, not-well-controlled or poorly controlled according to ACQ-5 score) at baseline (n=346). The median (IQR) ACQ-5 score at the end of the 6-month observation period was 0.6 (0.2-1.2) with a median (IQR) change from baseline to this time point of -1.4 (-2.2 to -0.6). The percentage of patients with poorly controlled asthma decreased from 74.3% (n=257) to 18.5% (n=64). These results were consistent with the results of the whole FAS population. (Table A4)

59.8% of subjects was treated with BDP/FF NEXThaler® 100/6 µg alone. Among subjects on MART, 30.4% (n=89) had at least one concomitant medication for asthma, while among subjects on maintenance only, 62.3% (n=81) had at least one concomitant medication for asthma. When considering the frequency of treatment combinations in MART group vs maintenance only, there was a significant difference in the concomitant use of SABA, which was equal to 4.1% in patients treated with MART compared to 50% in the maintenance-only group ($p<0.0001$).

Improvements in lung function

The NEWTON study also collected information about lung function during the observation period. According to the measurements available in the clinical practice, not all subjects had FEV₁, FEF_{25%-75%}, and PEF recordings at baseline and 6-month follow-up. Among the subjects with available data about FEV₁ (% of predicted) (n=150), the median change at 6 months in FEV₁ (% of predicted) pre-bronchodilator was 7.0 (IQR: -2.0 – 15.5) and was statistically significant ($p<0.0001$). Among the subjects with available data about FEF_{25%-75%}, at baseline and 6-month follow-up (n=100), the FEF_{25%-75%} (% of predicted) pre-bronchodilator significantly improved ($p<0.0001$). In addition, the median change of PEF (% of predicted) pre-bronchodilator at 6 months was 7.0 (IQR:

-5.0 – 19.3) among subjects with available data (n=125) and it was statistically significant (p<0.0001) (Table 2).

Improvements in QoL measured by the EQ-5D-5L index

Similarly to the asthma control levels also the QoL improved significantly. The EQ-5D-5L index increased in both subsets of subjects, who had available questionnaires at baseline and either 3-month follow-up (n=354) or 6 month-follow-up (n=391), from 0.881 to 0.970 and 0.887 to 1.000, respectively (p<0.0001 for both) (Tables 3 and 4).

Treatment adherence and satisfaction with the device

In the two subgroups of subjects who compiled the TAI questionnaire at enrolment and either 3-month follow-up (n=312) or 6-month follow-up (n=345) adherence to therapy improved and the percentages of the subjects in the category “good adherence” at baseline rose from 31.7% (n=99) to 50.0% (n=156) at 3-month follow-up and from 30.4% at baseline (n=105) to 49.9% (n=172) at 6-month follow-up (Figure 3). Adherence score increased from 46.0 at baseline to 49.5 at 3-month follow-up visit, and the improvement remained substantially maintained at the 6-month follow-up. The change was statistically significant (p<0.0001).

The improvement in adherence was consistent with overall satisfaction with the device. Among subjects who completed the structured interview with the 3 questions about their satisfaction with the BDP/FF NEXThaler® 100/6 µg (n=387), 81.1% (n=314) were completely or very satisfied with the ease of use, 83.7% (n=324) were completely or very satisfied with the delivered dose check, and 79.3% (n=307) were completely or very satisfied with the device in general at the end of observation period (Figure A1), with similar results at 3-month follow-up visit.

Safety and exacerbations

In the SAF population (n=609), 10.2% (n=62) of subjects experienced a TEAE and 4.3% (n=26) reported at least one TEAE related to BDP/FF NEXThaler® 100/6 µg. Overall, 2.1% of

subjects (n=13) reported at least one TEAE that led to treatment discontinuation. No TEAE related to BDP/FF NEXThaler® 100/6 µg leading to death were observed during the study period (Tables A5). The most frequent TEAEs (> 2.0%) were infections and infestations (3.3%, n=20), respiratory events (2.1%, n=13) and nervous system disorders (2.0%, n=12). As expected, the most frequent infections were COVID-19 and influenza (n=6, 1.0% and n=5, 0.8% respectively), while the most frequent respiratory events were asthma (n=7, 1.1%) and cough (n=4, 0.7%) (Table A6). Among the 421 special situations during the observation period, the majority (n=418) were caused by off-label use.

In the 12 months before the enrollment 79 subjects (13.0%) of the SAF population experienced moderate-to-severe exacerbations. At the end of observation, 21 subjects (3.4%) experienced moderate-to-severe exacerbations. 22 moderate-to-severe exacerbations occurred during the study period and resulted in either increase of the dosage (18.2%, n=4) or permanent withdrawal of the drug (13.6%, n=3). In most of the exacerbation cases (59.1%, n=13), however, the event did not affect the dosage. 2 out of 22 (9.1%) required admission to the emergency room and most of them (n=19, 86.4%) were resolved during the observation period (Table A7).

Discussion

According to GINA 2024, asthma control is assessed by two domains: symptom control and risk of adverse outcomes, including exacerbations. [1] The MART approach is considered a better approach for reducing asthma exacerbations compared to maintenance therapy, and this has, among other things, also been demonstrated with BDP/FF 100/6 µg. [24] For this reason, the National Heart, Lung and Blood Institute (NHLBI)/National Asthma Education and Prevention Program (NAEPP), the GINA recommendations, and the National Institute for Health and Care Excellence (NICE) guidelines advocate using a MART approach as preferred treatment.[25] In addition to exacerbation risk, symptom control is also important. [1, 26] In this context, BDP/FF NEXThaler® 100/6 µg, a patient-friendly and effective administration device, proved to be a reliable and well-tolerated tool for regular asthma treatment with a fixed dose combination of BDP/FF. The NEXThaler® was found to be non-inferior to extrafine BDP/FF treatments administered via pMDI

in terms of lung function, asthma control and use of rescue medication. [27] The favourable outcomes with NEXThaler® can be attributed to its extrafine formulation. Most inhalers, such as pMDIs and other DPIs, do not consistently produce particles small enough to reach the distal airways, which are also involved in the inflammatory process that characterize asthma and that may lead to a small airways disease. [28, 29] NEXThaler® produces aerosols with MMAD <2 µm, enhancing lung deposition and drug bioavailability.[30] This enables greater distal airway delivery and reduced oropharyngeal exposure, potentially limiting side effects and systemic absorption.[31] A pooled analysis from Austria confirmed the effectiveness and tolerability of extrafine BDP/FF in real-world settings, regardless of smoking status. [32]

In the NEWTON study, up to 66.1% of subjects significantly improved their level of asthma control score 6 months after starting treatment with BDP/FF NEXThaler® 100/6 µg. The proportion of subjects with not-well-controlled or poorly controlled asthma decreased from 87.6% to 43.3% at the 6-month follow-up. The improvements in ACQ-5 score were found even after those who had already reported well-controlled asthma at baseline were excluded from the analysis, with patients with poorly controlled asthma decreasing from 74.3% to 18.5%. This finding is not unexpected, given that the ACQ score is a patient-reported outcome (PRO), and therefore, discrepancies between the patients' perception and clinical evaluation may exist. The sensitivity analysis (excluding the well-controlled subgroup according to ACQ-score) confirmed that the improvement in ACQ-5 was consistent with that observed in the FAS population.

These changes were already visible to a similar extent at the 3-month visit indicating that asthma control had already improved quickly after the start of the treatment and then remained stable until the end of the study period. These observations are also consistent with other recent national studies: Bakakos and colleagues showed that more than 70% of subjects had well-controlled asthma 6 months after the start of BDP/FF NEXThaler® 100/6 µg treatment (based on ACQ-6 score). Similarly, in a study by Ulmenau and colleagues ACQ-7 in subjects treated with BDF/FF 100/6 µg pMDI scores changed significantly from baseline to the 6-month visit (1.05 ± 0.78 vs 3.05 ± 0.80 at baseline).[2, 33] It is noteworthy that NEWTON reported consistent results in a European population. About 70% of patients underwent MART during observation and 30%

293 maintenance only. Of note, the concomitant use of SABA in patients treated with MART was 4.1%
 294 compared to 50% in the maintenance only group ($p < 0.0001$). This is more aligned with current
 295 recommendations and in contrast to what emerged in a recent international survey, which reported
 296 that most patients using MART were also prescribed a rescue inhaler. [34] This may indicate a
 297 general proper knowledge and use of MART in the considered European countries.

298 The study found that the use of the extrafine BDP/FF NEXThaler® 100/6 µg led to
 299 improvements in pulmonary function, e.g. FEV₁ and FEF_{25%-75%}, during the observational period.
 300 These findings are consistent with other clinical trials, in which lung function and asthma control
 301 improved with the BDP/FF combination using pressurized metered-dose inhalers (pMDIs) or
 302 BDP/FF NEXThaler® 100/6 µg. [1,27, 35]

303 Although 60% of the subjects were overweight or obese, the treatment demonstrated
 304 significant effectiveness. This observation is of utmost importance considering that change in BMI
 305 is found to be an independent factor in the improvement of asthma control and a significant relation
 306 between the higher BMI (overweight or obese) and the worse ACQ-score. [36, 37]

307 Better asthma control, expressed by lower ACQ-5 scores, was found to be the most
 308 important predictor of better asthma-related QoL. [36] Similar to other studies, the NEWTON study
 309 showed that quality of life, captured by the EQ-5D-5L index, improved significantly from baseline to
 310 3-month and the median EQ-5D-5L index score at 6-month follow-up was equal to 1, corresponding
 311 to the maximum value for the scale. [2, 4]

312 Among subjects who completed the structured interview about their satisfaction with the
 313 device, most of them were satisfied in terms of ease of use and ability to check dose intake, with a
 314 general satisfaction equal to 79.3%.

315 The safety profile was in line with the summary of product characteristics.

316 As widely recognised, observational studies offer the opportunity to assess treatment
 317 effectiveness and safety in routine clinical practice, complementing evidence from randomized
 318 clinical trials (RCTs). [38] While RCTs focus on restricted populations under controlled experimental
 319 conditions, using specifically designed data collection tools, observational studies aim to gather
 320 information on broader populations and real-world scenarios that reflect routine clinical practice,

using data from everyday clinical settings. However, some limitations of the study should be considered: 1) the study centers were not randomly selected, potentially limiting the representativeness of the final sample. To enhance generalizability, sites were chosen from different countries. 2) Only subjects who were able to understand and independently complete the questionnaires were eligible according to exclusion criteria. This may have introduced a selection bias towards younger and healthier participants. 3) Subjects could initiate treatment no more than 14 days before enrolment, leading to the exclusion of those who had discontinued BDP/FF NEXThaler® 100/6 µg before. However, the risk of immortal-time bias should be limited considering the shortness of the period. In addition, study drug's effect during this short window is thought to be limited, according to clinical judgment. 4) Some clinical outcomes (i.e. lung functions) and PROs were affected by missing information, as is common in observational data collection. This may further limit the generalizability of the results. Nonetheless, the available data reflect the actual clinical practice in the participating centres and indicate a lower frequency of such clinical outcomes during the study visits. Importantly, sample size simulations accounted for these scenarios and the precision of the resulting estimates was deemed acceptable; 5) since only 67 subjects were current smokers, no specific analysis was performed to describe asthma control within this subgroup. However, an explorative analysis on asthma control improvement (not shown) indicated that the proportion of patients who improved was similar among current or former smokers and non-smokers. Finally, the focus of the study was to describe the response to the extrafine fixed-dose formulation of BDP/FF 100/6 µg delivered via the NEXThaler® in adults in a real-life context; therefore, the comparison with other formulations was out of scope.

Conclusion

The results of the NEWTON observational study confirm the effectiveness and safety of extrafine fixed combination of BDP/FF NEXThaler® 100/6 µg in European adults with uncontrolled moderate-to severe asthma in a real-world setting, leading to clinically relevant improvements in asthma control, QoL and pulmonary function. During the observation period the subjects reported high adherence to the treatment and satisfaction with the device.

Ethics Approval and Informed Consent

The Ethics Committee of each participating centre approved the study protocol before the study started. The informed consent for participation in the study and use of personal data were obtained from all subjects before any study-related procedures were performed.

Acknowledgments

The NEWTON Study was funded by Chiesi Italia S.p.A.

IQVIA Solutions Italy srl. contributed to the design, conduction, scientific support, clinical operations, data management, and statistical analysis of the study, with medical writing and editorial assistance provided by Daniela Longo, PhD, of PopMED. Luca Cavalieri and Giorgia Sedda (Chiesi Italia S.p.A) contributed to data interpretation and to the critical revision of the manuscript.

This manuscript was prepared according to the International Society for Medical Publication Professionals' "Good Publication Practice for Communicating Company-Sponsored Medical Research: GPP3". MedDRA® trademark is registered by ICH.

The authors are grateful to all subjects participating in this study.

Collaborators*

János Mucsi, Anca-Georgia Jäger, Hendrik Laßmann, Alberto Ricci, Athanasios Xanthopoulos, Cyril Maurer, Cecilia Calabrese, Ovidiu Fira-Mlădinescu, Doina Adina Todea, Walter Castellani, Francisco Javier Álvarez Gutiérrez, Barbara Canari Venturi, Stefano Nava, Lucio Michieletto, Maxime Sauvage, Claudia Lucia Toma, Giuseppe Arcoleo, Paride Morlino, Gabriella Gálffy, Angelo Guido Corsico, Antonio Ponticiello, Luisa Brussino, Carlos Martínez Rivera, Thomas Schultz, Bader Askar, Karl-Heinz Franz, Gianenrico Senna, Herve Pegliasco, Hermann Harald Gerhard Ingerl, Anna Sárközi, Alfio Pennisi, Olivier Lagrange, Pierachille Santus, Manuel Jorge Rial Prado, Ana Gómez-Bastero Fernández, Enzo Vincenzo Cannata, Naim Fourar-Laidi, Stefano Baglioni, Eugenio Sabato, Ibon Eguíluz Gracia. *sorted by descending frequency of evaluable patients.

Appendices

This paper includes also Supplementary material with Tables (A1-A6) and Figures (A1-A2) cited in the text.

Authors' contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. All authors confirm they consent in the publication of the manuscript.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request and with prior permission of Chiesi.

Abbreviations

ACQ-5: Asthma Control Questionnaire-5 items; BDP/FF: Beclometasone dipropionate/formoterol fumarate; BMI: Body mass index; BUD/F: Budesonide/formoterol; CRF: Case report form; DBP: Diastolic blood pressure; FEF25%-75%: Mean forced expiratory flow between 25% and 75% of FVC; FEV1: Forced expiratory volume in 1st second; FEV1/FVC: Forced expiratory volume in 1st second/forced vital capacity; FVC: Forced vital capacity; GINA: Global initiative for asthma; ICF: Informed consent form; ICS: Inhaled corticosteroid; LABA: Long-acting beta-2-agonist; LAMA: Long-acting muscarinic antagonist; LTRA: Leukotriene receptor antagonists; MART: Maintenance and reliever therapy; PEF: Peak Expiratory Flow; pMDI: Pressurized metered-dose inhaler; SAE: Serious adverse event; SABA: Short-acting beta-2-agonist; SBP: Systolic blood pressure; SD: Standard deviation.

399 **References**

- 400 1. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2024.
401 Update May 2024. Available from: www.ginasthma.org. Accessed June 2024.
- 402 2. Bakakos P, Chatziapostolou P, Katerelos P, et al. Extrafine beclometasone
403 dipropionate/formoterol NEXThaler on device usability, adherence, asthma control, and quality
404 of life: A Panhellenic prospective, non-interventional observational study in patients with
405 asthma—The NEXT-Step Study. *J Pers Med*. 12 (2022) 146.
- 406 3. Braido F, Brusselle G, Guastalla D, et al. Determinants and impact of suboptimal asthma control
407 in Europe: The International Cross-Sectional and Longitudinal Assessment on Asthma Control
408 (LIAISON) study. *Respir Res*. 17 (2016) 51.
- 409 4. Bateman ED, Boushey HA, Bousquet J, et al. Can guideline-defined asthma control be
410 achieved? The Gaining Optimal Asthma ControlL study. *Am J Respir Crit Care Med*. 170 (2004)
411 836-844.
- 412 5. Allegra L, Cremonesi G, Girbino G, et al.; PRISMA (PRospective Study on asthMA control)
413 Study Group. Real-life prospective study on asthma control in Italy: Cross-sectional phase
414 results. *Respir Med*. 106 (2012) 205–214.
- 415 6. Müller V, Gálffy G, Eszes N, et al. Asthma control in patients receiving inhaled corticosteroid
416 and long-acting beta2-agonist fixed combinations: A real-life study comparing dry powder
417 inhalers and a pressurized metered dose inhaler extrafine formulation. *BMC Pulm Med*. 11
418 (2011) 40.
- 419 7. Di Marco F. Today's improvement in asthma treatment: Role of MART and Easyhaler.
420 *Multidiscip Respir Med*. 15 (2020) 649.
- 421 8. Virchow JC, Poli G, Herpich C, et al. Lung deposition of the dry powder fixed combination
422 beclometasone dipropionate plus formoterol fumarate using NEXThaler® device in healthy

- 423 subjects, asthmatic patients, and COPD patients. *J Aerosol Med Pulm Drug Deliv.* 31 (2018)
424 269-280.
- 425 9. Watz H, Barile S, Guastalla D, Topole E, et al. Targeting the small airways with inhaled
426 corticosteroid/long-acting beta agonist dry powder inhalers: A functional respiratory imaging
427 study. *J Aerosol Med Pulm Drug Deliv.* 34 (2021) 280-292.
- 428 10. Papi A. Inhaled BDP/formoterol extra-fine combination: Evidence and future perspectives.
429 *Pneumologie.* 63 Suppl 2 (2009) S102-106.
- 430 11. Voshaar T, Spinola M, Linnane P, et al. Comparing usability of NEXThaler® with other inhaled
431 corticosteroid/long-acting β 2-agonist fixed combination dry powder inhalers in asthma patients.
432 *J Aerosol Med Pulm Drug Deliv.* 27 (2014) 363-370.
- 433 12. Schreiber J, Sonnenburg T, Luecke E. Inhaler devices in asthma and COPD patients: A
434 prospective cross-sectional study on inhaler preferences and error rates. *BMC Pulm Med.* 20
435 (2020) 222.
- 436 13. Ruessel K, Luecke E, Schreiber J. Inhaler devices in a geriatric patient population: A prospective
437 cross-sectional study on patient preferences. *Patient Prefer Adherence.* 14 (2020) 1811-1822.
- 438 14. Singh D, van den Berg F, Leaker B, et al. Comparison of the effect of beclometasone/formoterol
439 in asthma patients after methacholine-induced bronchoconstriction: a noninferiority study using
440 metered dose vs. dry powder inhaler. *Br J Clin Pharmacol.* 85 (2019) 729-736.
- 441 15. Corradi M, Chrystyn H, Cosio BG, et al. NEXThaler, an innovative dry powder inhaler delivering
442 an extrafine fixed combination of beclometasone and formoterol to treat large and small airways
443 in asthma. *Expert Opin Drug Deliv.* 11 (2014) 1497-1506.
- 444 16. Braido F, Arnaboldi E, Barile S, et al. BDP/FF NEXThaler to improve asthma control status in
445 the real world: The NEWTON study. *J Asthma Allergy.* 16 (2023) 1177-1186.
- 446 17. Public Policy Committee, International Society of Pharmacoepidemiology. Guidelines for Good
447 Pharmacoepidemiology Practices (GPP). *Pharmacoepidemiol Drug Saf.* 25 (2016) 2-10.
- 448 18. Juniper EF, O'Byrne PM, Guyatt GH, et al. Development and validation of a questionnaire to
449 measure asthma control. *Eur Respir J.* 14 (1999) 902-907.
- 450 19. Juniper EF, Svensson K, Mörk AC, Ståhl E. Measurement properties and interpretation of three
451 shortened versions of the asthma control questionnaire. *Respir Med.* 99 (2005) 553-558.

- 452 20. Juniper EF, Bousquet J, Abetz L, Bateman ED. Identifying 'well-controlled' and 'not well-
453 controlled' asthma using the Asthma Control Questionnaire. *Respir Med.* 100 (2006) 616-621.
- 454 21. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level
455 version of EQ-5D (EQ-5D-5L). *Qual Life Res.* 20 (2011) 1727-1736.
- 456 22. Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared
457 to the EQ-5D-3L across eight patient groups: A multi-country study. *Qual Life Res.* 22 (2013)
458 1717-1727.
- 459 23. Plaza V, Fernández-Rodríguez C, Melero C, et al.; TAI Study Group. Validation of the 'Test of
460 the Adherence to Inhalers' (TAI) for asthma and COPD patients. *J Aerosol Med Pulm Drug
461 Deliv.* 29 (2016) 142-152.
- 462 24. Papi A, Corradi M, Pigeon-Francisco C, et al. Beclometasone-formoterol as maintenance and
463 reliever treatment in patients with asthma: A double-blind, randomised controlled trial. *Lancet
464 Respir Med.* 1 (2013) 23-31.
- 465 25. National Institute for Health and Care Excellence (NICE) Asthma: diagnosis, monitoring and
466 chronic asthma management (BTS, NICE, SIGN) 2024
- 467 26. Cloutier MM, Baptist AP, Blake KV, et al. 2020 Focused Updates to the Asthma Management
468 Guidelines: A report from the National Asthma Education and Prevention Program Coordinating
469 Committee Expert Panel Working Group. *J Allergy Clin Immunol.* 147 (2021) 1528-1530.
- 470 27. Kanniess F, Scuri M, Vezzoli S, et al. Extrafine beclomethasone/formoterol combination via a
471 dry powder inhaler (NEXThaler®) or pMDI and beclomethasone monotherapy for maintenance
472 of asthma control in adult patients: A randomised, double-blind trial. *Pulm Pharmacol Ther.* 30
473 (2015) 121-127.
- 474 28. Lavorini F, Pedersen S, Usmani OS, et al., Dilemmas, Confusion, and Misconceptions Related
475 to Small Airways Directed Therapy. *Chest.* 2017 Jun;151(6):1345-1355.
- 476 29. Cottini M, Lombard C, Micheletto C. Small airway dysfunction and bronchial asthma control:
477 the state of the art. *Asthma Res Pract* 2015;1:13
- 478 30. Tamm M, et al. Inhaled corticosteroid and long-acting β_2 -agonist pharmacological profiles:
479 effective asthma therapy in practice *Respir Med* 2012;106 Suppl1:S9-19
- 480 31. Usmani OS, Scichilone N, Mignot B, Belmans D, et al. Airway Deposition of Extrafine Inhaled
481 Triple Therapy in Patients with COPD: A Model Approach Based on Functional Respiratory

- 482 Imaging Computer Simulations. *International Journal of Chronic Obstructive Pulmonary*
 483 *Disease* 2020;15 2433–2440
- 484 32. Renner A, Marth K, Breyer-Kohansal R et al. Combined analysis of five non-interventional
 485 studies of the effectiveness, tolerability, and safety of the extrafine fixed dose
 486 beclomethasone/formoterol combination in the treatment of asthma in Austria. *Respir Med.*
 487 2023;207:107097
- 488 33. Ulmenau R, Boju S, Vittos O. Assessment of symptoms control, pulmonary function, and related
 489 quality of life in asthmatic patients treated with extrafine beclomethasone
 490 dipropionate/formoterol fumarate 100/6 µg pMDI: Results of a multicenter observational study
 491 in Romania (ALFRESCO Study). *J Asthma Allergy.* 15 (2022) 919-933.
- 492 34. Chapman KR, Canonica GW, Lavoie KL, et al. Patients' and physicians' perspectives on the
 493 burden and management of asthma: Results from the APPaRENT 2 study. *Respir Med.* 201
 494 (2022) 106948. doi:10.1016/j.rmed.2022.106948.
- 495 35. Huchon G, Magnussen H, Chuchalin A, et al. Lung function and asthma control with
 496 beclometasone and formoterol in a single inhaler. *Respir Med.* 103 (2009) 41-49.
- 497 36. Luis G, Pétré B, Schieich F, et al. Predictors of change in asthma-related quality of life: A
 498 longitudinal real-life study in adult asthmatics. *Qual Life Res.* 32 (2023) 1507–1520.
- 499 37. Lavoie KL, Bacon SL, Labrecque M, et al. Higher BMI is associated with worse asthma control
 500 and quality of life but not asthma severity. *Respir Med.* 100 (2006) 648-657.
- 501 38. Gershon AS, Jafarzadeh SR, Wilson KC, Walkey AJ. Clinical knowledge from observational
 502 studies: Everything you wanted to know but were afraid to ask. *Am J Respir Crit Care Med.* 198
 503 (2018) 859-867.
- 504

Figure 1. Patient disposition

Safety Set (SAF): all enrolled subjects who signed informed consent form and received at least one administration of BDF/FF Nexthaler® 100/6 µg; Full Analysis Set (FAS): all eligible subjects who had a valid baseline assessment of ACQ-5 and at least one post-baseline assessment of ACQ-5 during the 6-month observation period (i.e. Evaluable Subjects);. The analysis of safety endpoints was performed in the SAF set. All other analyses (including primary and secondary endpoints) were performed in the FAS.

Table 1 Demographic and clinical Characteristics at baseline

Characteristics	Evaluable subjects (N=423)
Gender (n, %)	
Male	136 (32.2%)
Female	287 (67.8%)
Age, years	
Median (IQR)	49.0 (34.0-61.0)
Mean (SD)	48.1 (17.2)
Age classes, n (%)	
18-34 years old	107 (25.3%)
35-59 years old	194 (45.9%)
>=60 years old	122 (28.8%)
Smoking status, n (%)	
Non-smoker	275 (65.0%)
Current smoker	67 (15.8%)
Ex-smoker	81 (19.1%)
Body Mass Index (BMI) classes, n (%)	N=411
Underweight	7 (1.7%)
Normal weight	150 (36.5%)
Overweight	131 (31.9%)
Obese	123 (29.9%)
Median time since first asthma diagnosis, years, (IQR)	N=413 8.7 (1.8-19.9)
Moderate or severe exacerbation in the previous 12 months, n (%)	N=419
Yes	60 (14.3%)
No	359 (85.7%)

ACQ-5 score	
Median (IQR)	2.0 (1.2-3.0)

The percentages were calculated excluding the missing/unknown (unk) data for each considered variable (see the number of available observations, when reported [N=]).

ACQ-5: Asthma Control Questionnaire-5 items; IQR: interquartile range

Figure 2 Improvements in asthma according to ACQ-5 score. Baseline vs 3-month and vs 6-month follow-ups.

ACQ-5: Asthma Control Questionnaire-5 items; A) The McNemar-Bowker test was used to compare the distribution of asthma control categories at baseline and 6-month follow-up. B) The ACQ-5 score ranges between 0 (totally controlled) and 6 (extremely poorly controlled). The Wilcoxon Signed Rank test for paired samples was used to test median differences in ACQ-5 score between baseline and 3-month follow-up and between baseline and 6-month follow-up.

Journal Pre-proof

Table 2 Pulmonary Function pre-bronchodilator at baseline and 6-month follow-up

	Baseline	6-month follow-up	Change at 6-month vs baseline
FEV₁ actual value (L) (n=151) Median (IQR)	2.5 (1.9-3.0)	2.7 (2.2-3.3)	0.1 (-0.1-0.4) *
FEV₁ (% of predicted) (n=150) Median (IQR)	86.0 (73.2-92.0)	93.0 (83.0-104.0)	7.0 (-2.0-15.5)*
FVC actual value (L) (n=151) Median (IQR)	3.3 (2.5-3.9)	3.3 (2.8-4.1)	0.1 (-0.1-0.4) *
FVC (% of predicted) (n=151) Median (IQR)	92.0 (80.0-101.0)	97.0 (88.0-106.0)	4.0 (-2.0-13.0)*
FEV₁/FVC ratio (n=151) Median (IQR)	0.8 (0.7-0.8)	0.8 (0.7-0.9)	0.0 (-0.0-0.1)§
FEF_{25%-75%} (L/s) (n=102) Median (IQR)	2.3 (1.6-3.1)	3.0 (1.9-3.6)	0.3 (-0.2-1.0)^
FEF_{25%-75%} (% of predicted) (n=100) Median (IQR)	67.5 (53.0-85.5)	80.0 (60.0-99.5)	8.0 (-4.5-25.5)*
PEF (L/min) (n=136) Median (IQR)	365.4 (234-471.0)	388.5 (316.7-512.8)	28.3 (-18.6-92.0)*
PEF (% of predicted) (n=125) Median (IQR)	78.0 (61.0-97.0)	91.0 (74.0-102.0)	7.0 (-5.0-19.3)*

*p<0.0001; § p=0.009; ^ p=0.0002. FEV₁: Forced expiratory volume in 1st second; FVC: Forced vital capacity; FEV₁/FVC: Forced expiratory volume in 1st second/forced vital capacity; FEF_{25%-75%}: Mean forced expiratory flow between 25% and 75% of FVC; PEF: Peak Expiratory Flow; IQR: interquartile range. The Wilcoxon Signed Rank test for paired samples was used to test median differences in lung function parameters between baseline and 6-month follow-up.

Table 3 Improvements of QoL after 3-month according to EQ-5D-5L index

	Evaluable subjects (N=354)		
EQ-5D-5L INDEX	Baseline	3-month follow-up	p-value
Median (IQR)	0.881 (0.799-0.970)	0.970 (0.913-1.000)	<0.0001

EQ-5D-5L: EuroQol 5-dimension 5-level; IQR: interquartile range. The Wilcoxon Signed Rank test for paired samples was used to test median differences in EQ-5D INDEX value between 3-month follow-up and baseline. Median, IQR, and test were obtained on evaluable subjects with available information on EQ-5D-5L at baseline and at 3-month follow-up.

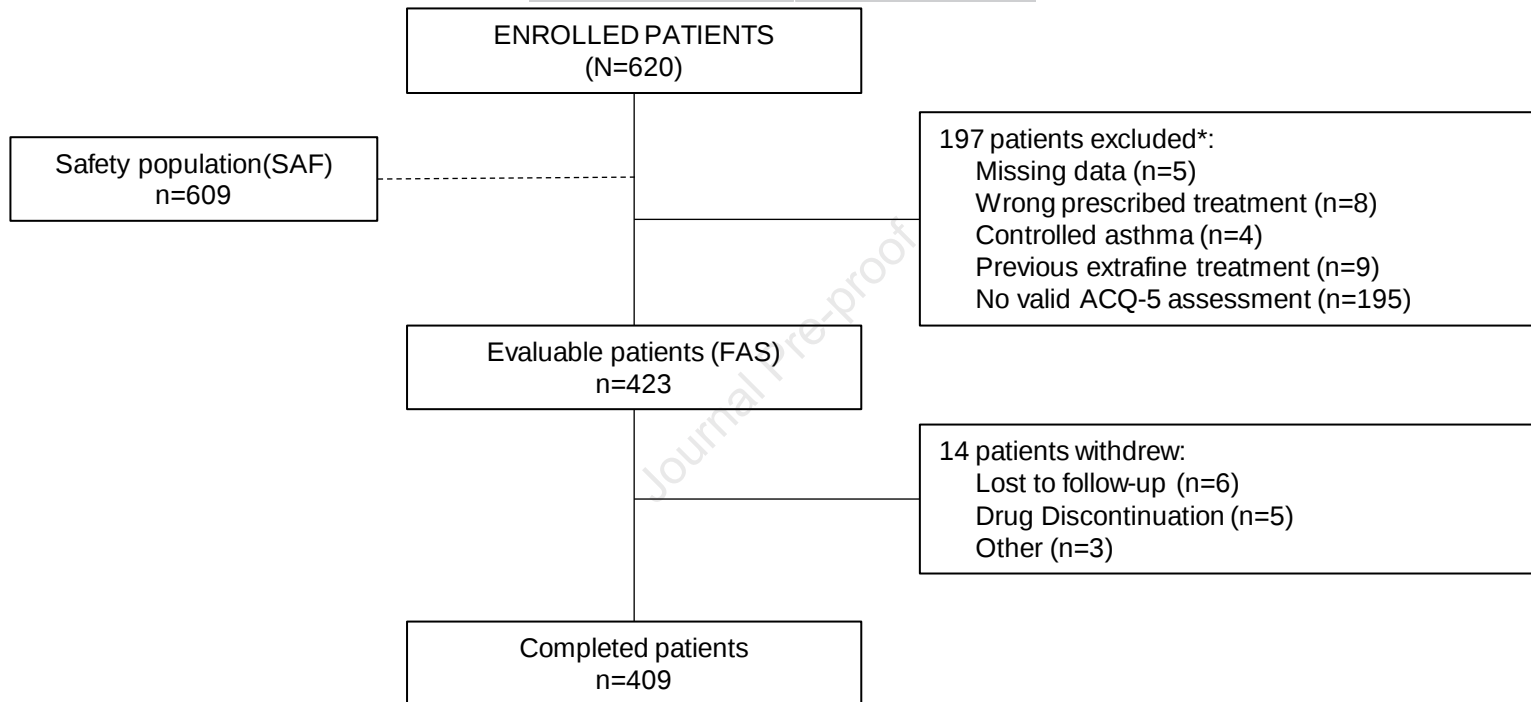
Table 4 Improvements of QoL after 6-month according to EQ-5D-5L index

	Evaluable subjects (N=391)		
EQ-5D-5L INDEX	Baseline	6-month follow-up	p-value
Median (IQR)	0.887 (0.801-0.907)	1.000 (0.913-1.000)	<0.0001

EQ-5D-5L: EuroQol 5-dimension 5-level; IQR: interquartile range. The Wilcoxon Signed Rank test for paired samples was used to test median differences in EQ-5D INDEX value between 6-month follow-up and baseline. Median, IQR, and test were obtained on evaluable subjects with available information on EQ-5D-5L at baseline and at 6-month follow-up.

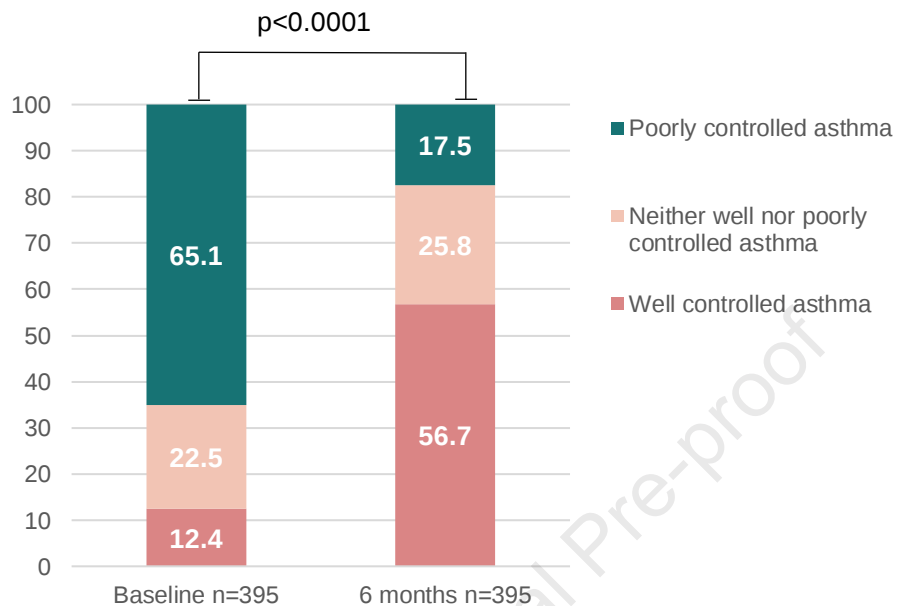
Figure 3 Level of Adherence to therapy according to the TAI questionnaire

Journal Pre-proof

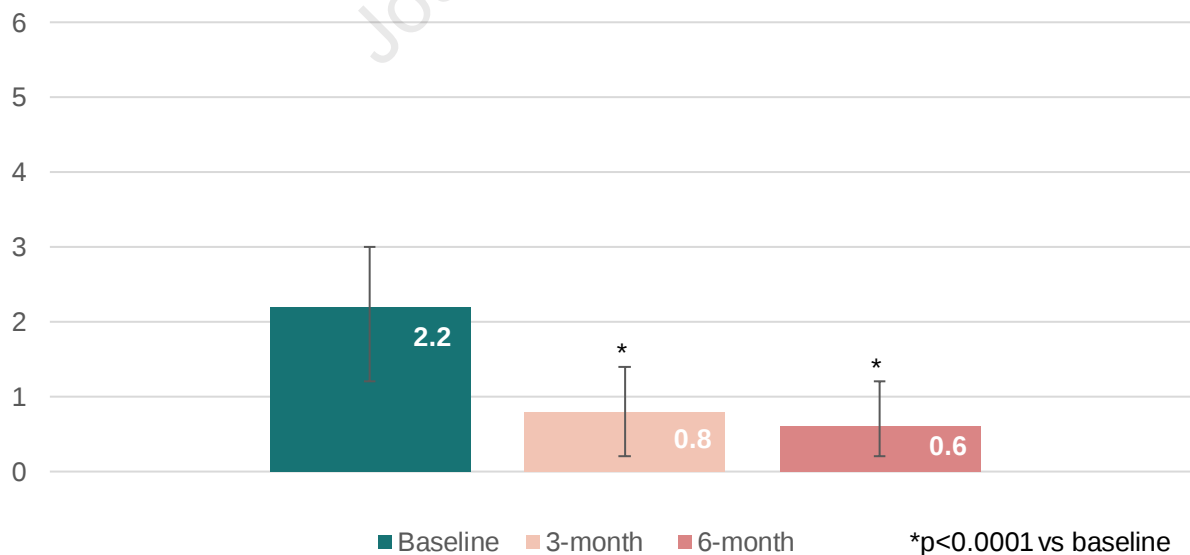


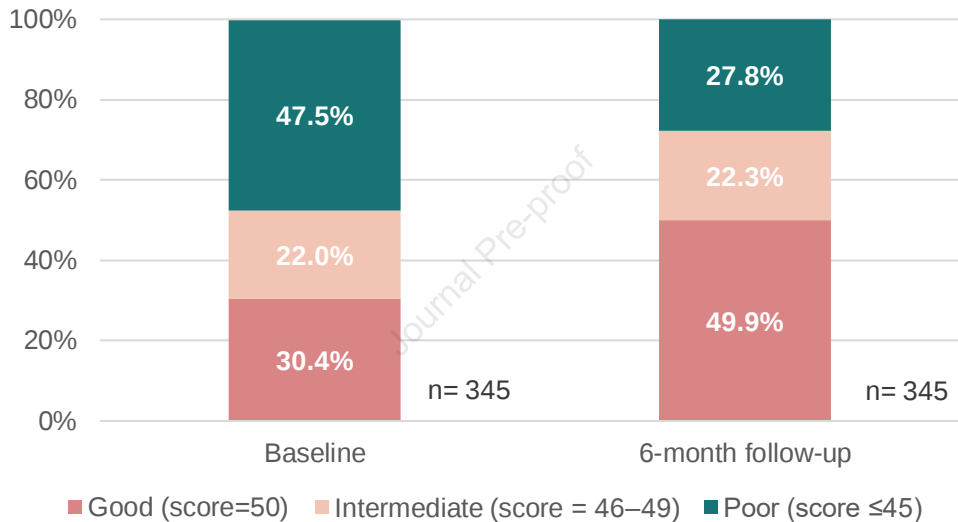
* Patients could be excluded for more than one reason

A) Asthma control level



B) ACQ-5 score in evaluable subjects with ACQ-5 available in the three study time points (n=331)





1 **ORIGINAL RESEARCH**

2 Braido F et al

3 **Real-world use of beclometasone dipropionate and**
4 **formoterol fumarate NEXThaler® and asthma control**
5 **among adult asthmatic patients in Europe: The results**
6 **of the NEWTON Study**

7 Fulvio Braido¹, Kai-Michael Beeh² (ORCID ID 0000-0001-9067-118X), Carolina Cisneros
8 Serrano³ (ORCID ID 0000-0003-4297-4199), Anh Tuan Dinh-Xuan⁴ (ORCID ID 0000-0001-8651-
9 5176), Lilla Tamási⁵, Antigona Trofor⁶ (ORCID ID: 0000-0003-3252-7715), Eleonora Ingrassia⁷
10 (ORCID ID 0000-0002-6597-0556), Alessio Piraino⁸ (ORCID ID 0000-0002-8029-2159), Cristiano
11 Caruso⁹ (ORCID ID 0000-0001-7631-029X) on behalf of the NEWTON study group¹⁰

12
13 ¹IRCCS Ospedale Policlinico San Martino, Università di Genova, DiMI, Genoa, Italy; ²Insaf
14 Respiratory Research Institute, Taunusstein, Germany; ³Department of Neumology, University
15 Hospital La Princesa, Madrid, Spain; ⁴Department of Respiratory and Sleep Medicine, Cochin
16 Hospital, Université Paris Cité, Paris, France; ⁵Department of Pulmonology, Semmelweis
17 University, Budapest, Hungary; ⁶“Grigore T. Popa” University of Medicine and Pharmacy, Iasi,
18 Romania – Clinic Hospital of Pulmonary Diseases, Iasi, Romania; ⁷Chiesi Italia S.p.A., Parma,
19 Italy; ⁸Chiesi Farmaceutici S.p.A., Global Medical Affairs - AIR Parma, Italy; ⁹UOSD Allergy and
20 Clinical Immunology, Fondazione Policlinico A. Gemelli, IRCCS, Catholic University of Sacre
21 Heart, Rome, Italy; ¹⁰see Collaborators.

22
23
24 Correspondence:

25 Fulvio Braido, Respiratory Diseases and Allergy Clinic, IRCCS, Ospedale Policlinico San Martino,
26 Genova, Italy, University of Genoa.
27 Email fulvio.braido@unige.it
28 ORCID ID: 0000-0003-2460-4709

29 **Highlights:**

- 30 • NEWTON is an observational study on asthma patients in Europe.
- 31 • Patients are followed for up to 6 months from start of BDP/FF NEXThaler® 100/6 µg.
- 32 • Rapid and sustained asthma control with BDP/FF NEXThaler® 100/6 µg is found.
- 33 • Poorly controlled asthma dropped from 65.1% to 17.5% at the end of the study.
- 34 • No new safety concerns emerged during the study, confirming treatment tolerability.

Declaration of interests

- ☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
- ☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Alessio Piraino reports article publishing charges and writing assistance were provided by Chiesi Italia S.p.A. Fulvio Braido reports financial support was provided by Chiesi Farmaceutici SpA. Carolina Cisneros Serrano reports financial support was provided by Chiesi España SA. Fulvio Braido reports a relationship with GSK that includes: board membership and speaking and lecture fees. Fulvio Braido reports a relationship with Chiesi that includes: board membership and speaking and lecture fees. Fulvio Braido reports a relationship with Menarini group that includes: board membership and speaking and lecture fees. Fulvio Braido reports a relationship with Astra Zeneca that includes: board membership and speaking and lecture fees. Fulvio Braido reports a relationship with Sanofi that includes: board membership and speaking and lecture fees. Fulvio Braido reports a relationship with Regeneron that includes: board membership and speaking and lecture fees. Kai-Michael Beeh reports a relationship with Astra Zeneca that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Kai-Michael Beeh reports a relationship with Chiesi Farmaceutici SpA that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Kai-Michael Beeh reports a relationship with Bosch Healthcare Solutions GmbH that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Kai-Michael Beeh reports a relationship with Berlin-Chemie AG that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Kai-Michael Beeh reports a relationship with Sanofi-Aventis Deutschland GmbH that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Kai-Michael Beeh reports a relationship with GlaxoSmithKline Inc that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Carolina Cisneros Serrano reports a relationship with Sanofi SA that includes: consulting or advisory, funding grants, non-financial support, speaking and lecture fees, and travel reimbursement. Carolina Cisneros Serrano reports a relationship with GlaxoSmithKline SpA that includes: consulting or advisory and speaking and lecture fees. Carolina Cisneros Serrano reports a relationship with AstraZeneca that includes: consulting or advisory, funding grants, speaking and lecture fees, and travel reimbursement. Anh Tuan Dinh-Xuan reports a relationship with Boehringer Ingelheim that includes: speaking and lecture fees. Anh Tuan Dinh-Xuan reports a relationship with GSK that includes: speaking and lecture fees. Anh Tuan Dinh-Xuan reports a relationship with Menarini that includes: speaking and lecture fees. Anh Tuan Dinh-Xuan reports a relationship with Sanofi that includes: speaking and lecture fees. Eleonora Ingrassia reports a relationship with Chiesi Italia that includes: employment. Alessio Piraino reports a relationship with Chiesi Farmaceutici SpA that includes: employment. Kai-Michael Beeh declares that, in the past five years, the institution has received compensation for the conduct of clinical trials by the following corporations: AstraZeneca, Bosch Healthcare Solutions GmbH, Chiesi, GSK, Novartis, Sterna. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.