e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15 (6); 1317-1326

Original Research Article

Efficacy and Safety Assessment of Indacaterol Acetate and Glycopyrronium Bromide Combination in Patients of Bronchial Asthma

Md Hanzalah[1], Mohd Ashraf Alam[2], S. Ziaur Rahman[3], Zuber Ahmad[4], Raihan Mannan[5*]

[1]Department of Pharmacology, Government Medical College, Bettiah, West Champaran, Bihar;
[2]Department of Pharmacology, L. N Medical College, Indore, MP;
[3]Department of Pharmacology, Jawaharlal Nehru Medical College & Hospital, Aligarh Muslim University, Aligarh;
[4]Department of T.B and Respiratory Diseases, Jawaharlal Nehru Medical College & Hospital, Aligarh Muslim University, Aligarh;
[5]Assistant Professor, Department of Physiology, All India Institute of Medical Sciences, Patna

Received: 20-03-2023 / Revised: 11-04-2023 / Accepted: 05-05-2023
Corresponding author: Dr. Raihan Mannan
Conflict of interest: Nil

Abstract:

Background: Asthma in the bronchi is a severe problem, affecting 18% of the global population. Asthma and chronic obstructive pulmonary disease (COPD) were with indacaterol, a new beta-2 agonist, and glycopyrronium, a muscarinic receptor antagonist. Both medications have shown promise in treating asthma, but their potential synergistic impact has to be studied.

Aims: The present study aimed to assess the efficacy and safety of combined indacaterol acetate (110µg) and glycopyrronium bromide (50µg) 'IND-GLY' in patients of mild to moderate bronchial asthma.

Methods: In this trial, we used a randomized, prospective, open-label design. Fifty-seven patients were included in the research and given IND-GLY via dry powder inhaler once daily. Evaluation of pulmonary function test (PFT) and symptom score was used to evaluate effectiveness. At the start, after 45 minutes, after 21 hours, on days 3, 7, 14, and 28, we measured forced expiratory volume in a 1-second (FEV1). Researchers created the Naranjo Adverse Drug Reaction (A.D.R.) Probability Scale to quantify the chance of adverse medication responses.

Results: The study showed that there were significant improvements in FEV_1 ($p<0.05$) and clinical symptom score ($p<0.05$) compared to the baseline values.

Conclusions: It was determined that IND-GLY is clinically effective and safe in individuals with mild to moderate bronchial asthma. There was evidence that the treatment was helping all hours of the day.

Keywords: Bronchial asthma, β-2 agonist, Indacaterol acetate, muscarinic receptor antagonist, Glycopyrronium bromide.

Introduction

Global Initiative for Asthma (GINA) survey in 2022 refers to bronchial asthma as a chronic airway inflammatory disease that affects 1–18% of people worldwide and continues [1]. The heterogeneous illness is characterized by respiratory symptoms such as uneasiness while breathing, chest tightness, cough, and wheezing that vary in intensity and over time. These recurrent incidences are connected with airflow restrictions that may be reversible either after treatment or spontaneously [1]. The symptomatic variations are triggered by factors like exposure to allergens or irritants, exercise, changes in weather, or viral respiratory infections [2]. The patient may be asymptomatic for days or even months and then show severe symptoms without warning. The sudden exacerbation of the disease can be life-threatening [3]. Approximately 30% of death occurs in asthma patients with infrequent symptoms [1].

Although asthma is non-curable, suppressing the severity of asthmatic inflammations can help patients lead an active life [4]. The asthmatic symptoms are managed with inhaled medications supplied through inhalers. The inhalers are categorized as bronchodilators and steroids [4]. Bronchodilators relax the lungs muscles and widen the respiratory tract, thus relieving the symptoms. On the other hand, inhaled corticosteroids reduce inflammation in the airways. However, these drugs are under-prescribed to date [5].

It is evident from regular pharmacological practice that long-acting bronchodilators possess higher efficacy than short-acting forms. Long-acting β-2 adrenergic agonists (LABA) and Long-acting muscarinic antagonists (LAMA) are used as frontline drugs for the treatment of bronchial asthma [6]. A dual combination of LABA and LAMA has been more potent than mono-therapy. Hence, combinatorial therapy has been approved to significantly reduce asthmatic sudden outbreak and improve lung function [6-8].

Indacaterol and glycopyrronium are the Food and Drug Administration (F.D.A.) approved LABA and LAMA drugs, respectively [9-12]. Indacaterol loosens, broadens the airway passage, and aids normal breathing [12]. Glycopyrronium reduces the mucous secretions in the respiratory tract [11]. The combination of indacaterol acetate and glycopyrronium bromide inhaled once per day in a single device, was the first dual bronchodilator approved in Japan and Europe in 2013 for treatment in Chronic Obstructive Pulmonary Disease (COPD) [13, 14]. However, the combined use of indacaterol and glycopyrronium for the treatment of bronchial asthma falls short of expectations. Furthermore, although inhaled glycopyrronium has not yet been approved for use in asthma, it is now being considered for this condition [15]; therefore, a more investigational study is warranted. Patients with mild to severe bronchial asthma were included in this trial to assess the effectiveness and safety of a combination of indacaterol acetate (110 g) and glycopyrronium bromide (50 g) (IND-GLY).

Materials and Methods

Design of the study: A conducted prospective research with no restrictions on participant disclosure.

Settings

The study was carried out on the Bronchial asthma patient, diagnosed clinically and spirometrically attending O.P.D of T.B and Respiratory diseases. Institutional Ethics Committee approved the study protocol of J.N. Medical College & Hospital, A.M.U, Aligarh, on 18/05/2017 (629/FM/

18.05.2017). The registration number for the trial obtained from Clinical Trials Registry-India was CTRI/2018/05/014079.

Target population

The study target population was patients visiting T.B. and Respiratory Disease, Out Patient Department (O.P.D.) who were clinically and spirometrically diagnosed with bronchial asthma. All trial participants who met inclusion and exclusion criteria provided written informed permission before enrollment. Patients received 'IND-GLY' inhalational route through dry powder inhaler once a day for four weeks.

Inclusion criteria

Adults aged 18 to 65 who sought medical assistance against chest tightness and cough, particularly at night or in the early morning, with a documented spirometric diagnosis of asthma as per GINA guidelines, were included [1].

Exclusion criteria

Patients with an acute episode of exacerbation demanding systemic steroid or hospitalization; patients requiring intubation for severe asthma; patients whose clinical condition worsened by systemic corticosteroid administration; patients with a history of chronic lung disease other than asthma i.e., COPD, sarcoidosis, I.L.D. (Interstitial Lung Disease) and pregnant and lactating mothers were excluded.

Sample size

The percentage increase or decrease in forced expiratory volume in 1 second (FEV1) was used as the primary variable for the sample size calculation. The alpha-error threshold was set at 5%, while the power was set at 80% [16]. Out of 60 patients enrolled, 3 failed to report on subsequent visits and were excluded from the study. The study proceeded further with the remaining 57 patients. Patients were diagnosed of asthma as per GINA guidelines. Once a daily dose of IND-GLY has been recommended, the patient should take the medication at the same time every day. Patients with a forced expiratory volume in one second (FEV1) between 60% and 80% of the expected value were eligible for the trial, and they were not allowed to use any additional bronchodilators. [17].

Efficacy assessments

The efficacy of 'IND-GLY' was assessed by changes in spirometric parameter FEV_1 and improvement in the symptoms score pre-and post-treatment. Breathlessness, chest tightness, coughing, and nighttime insomnia were included in the list of symptoms and assigned a score between 0 and 5. Spirometric parameters and symptom scores were recorded before initiating the treatment at intervals of 45 minutes, 21 hours, 3^{rd}, 7^{th}, $14^{th,}$ and 28^{th} days post-treatment. The same spirometry tools were utilized throughout the research, and the tests were carried out following a Standard Operative Procedure (S.O.P.). Testing of lung capacity was performed using SPIROLAB III. Spirograms were evaluated for quality and consistency. Three good spirograms were used to calculate the optimal FEV1 levels. The combination's pre and post-treatment data were analyzed by appropriate tests using SPSS software (version 23).

Safety assessments

At each checkup, the researcher recorded any unpleasant occurrences the patient experienced or witnessed. The adverse drug responses were graded according to their onset and severity and were ranked on the Naranjo A.D.R. (Adverse Drug Reaction) Probability Scale. On day 1 and day 28 we did a complete physical examination, including taking all of your vitals.

Results

'IND-GLY' dual drug therapy was given to 57 patients. The age of selected patients varied from 18 to 65 years. Mean age of the patients was 47.4 years. From those, 39

were males and 18 females. Out of them, 21 (19.6%) were smokers. In terms of pack year, 14 patients (13.08%) had smoked for <5 pack years, and 7 (6.54%) had smoked for 5-10 pack years.

Efficacy assessment of 'IND-GLY' inhalation therapy

The present data showed that inhalation of 'IND-GLY' once a day for four weeks enhanced spirometric variables in asthma patients at 45 minutes and 21 hour and on 3rd, 7th, 14th and 28th days of treatment. There was statistically significant improvement in FEV_1 in comparison to baseline value. Mean ± S.D. of baseline and post spirometric values and p- values of different variables are detailed in Table 1.

Table 1: FEV_1 at different time and days of indacaterol - glycopyrronium inhalation in patients under investigation

Days of observation	Mean FEV_1 (in Litres); (n=57)	p- value
Baseline	1.6442 ± 0.65	---
At 45 min	1.7598 ± 0.67	0.000
At 21 hour	1.7818 ± 0.66	0.000
Day 3	1.7721 ± 0.64	0.000
Day 7	1.7818 ± 0.62	0.000
Day 14	1.7728 ± 0.62	0.000
Day 28	1.7577 ± 0.62	0.000

(Note: The data are presented as mean ± S.D.; p< 0.05 has been considered as significant)

when compared to respective baseline level. The clinical improvement was calibrated on a symptom score based on cough, chest tightness, shortness of breath and night time sleep deprivation. The result revealed decrease in symptom score as compared to baseline for 4 week treatment. Thus, significant improvement in clinical symptoms was observed post-treatment. Improvement of symptom scores on different days of observation has been depicted in Figure 1.

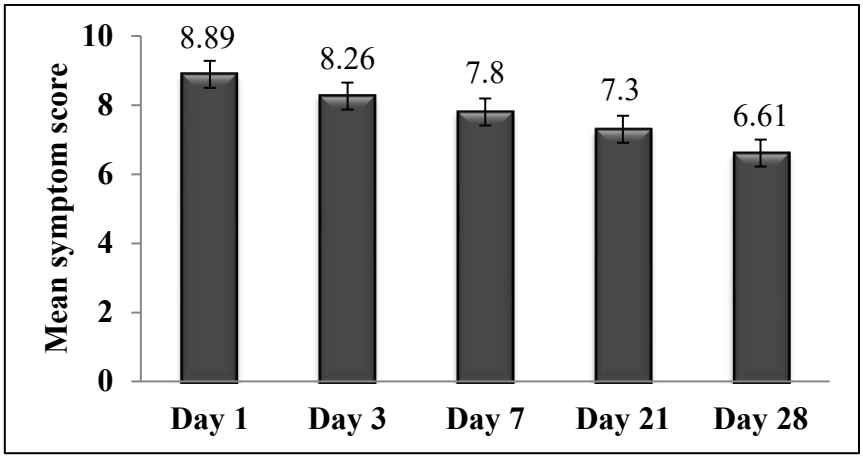

Figure 1: Symptom score of investigated patients on 1st, 3rd, 7th, 21st and 28th day of treatment (Note: The data are presented as mean ± S.D.; p < 0.05 has been considered as significant.)

Safety assessment of 'IND-GLY' drug

Safety assessment in patients under investigation was achieved by monitoring the heart rate, blood pressure (B.P.) and haematological parameters during the study. The result interpreted that all the monitored parameters were within the

normal limit even after 28 days of 'IND-GLY' medication. Heart rate is the number of times heart beat per minute. This can be tracked by pulse rate. No significant increase in the heart rate was evident during the study. In addition, there was no significant effect on blood pressure before and after treatment in selected asthma patients (Table 2).

Table 2: Effect of the treatment on pulse rate and blood pressure

Variables	Duration	'IND-GLY' (110/50 µg) treatment effect	p- value
Pulse (beat/min)	**Baseline**	74.59 ± 4.60	0.181
	After 28 days	77.73 ± 4.24	0.124
BP-Systolic (mmHg)	**Baseline**	128.49 ± 9.54	0.198
	After 28 days	130.17 ± 8.65	0.212
BP-Diastolic (mmHg)	**Baseline**	81.40 ± 4.87	0.376
	After 28 days	81.71 ± 4.35	0.665

(Note: The data are presented as mean ± S.D.; $p < 0.05$ has been considered as significant.)

The haematological parameters included for safety assessment and the outcome of the study has been shown in Table 3. No significant differences in haematological indices were observed between the baseline and post 28 days of medication.

Table 3: Effect of the treatment on different haematological parameters

S. No	Haematological parameters	Duration	'IND-GLY' (110/50 µg) treatment effect	p- value
1	**Hb (g/dl)**	**Baseline**	11.72 ± 1.57	0.911
		After 28 days	11.84 ± 1.3	0.604
2	**R.B.C. (10^6/µL)**	**Baseline**	5.60 ± 2.17	0.823
		After 28 days	5.49 ± 1.13	0.036
3	**WBC (10^3/µL)**	**Baseline**	5.70 ± 2.16	0.007
		After 28 days	5.74 ± 2.08	0.004
4	**Platelets (10^3/µL)**	**Baseline**	217.63 ± 44.18	0.111
		After 28 days	224.22 44.77	0.407
5	**Serum glucose (mg/dl)**	**Baseline**	114.69 ± 15.42	0.907
		After 28 days	115.60 ± 13.24	0.929
6	**BUN (mg/dl)**	**Baseline**	20.80 ± 7.01	0.585
		After 28 days	21.27± 6.41	0.464
7	**Creatinine (mg/dl)**	**Baseline**	1.17 ± 0.18	0.215
		After 28 days	1.23 ± 0.25	0.179
8	**Bilirubin (mg/dl)**	**Baseline**	1.02 ± 0. 32	0.176
		After 28 days	1.03 ± 0.34	0.011
9	**A.S.T. (U/L)**	**Baseline**	28.71 ± 14.70	0.170
		After 28 days	28.63± 14.4	0.011
10	**A.L.T. (U/L)**	**Baseline**	46.77 ± 21.11	0.170
		After 28 days	45.98 21.72	0.070
11	**A.L.P. (U/L)**	**Baseline**	80.42 ± 13.12	0.014
		After 28 days	80.49 ± 13.13	0.120

(Note: The data are presented as mean ± S.D.; $p < 0.05$ has been considered as significant.)

Hb: Haemoglobin; R.B.C.: Red Blood Cells; WBC: White Blood Cells; BUN: Blood Urea Nitrogen; A.S.T.: Aspartate Aminitransferase; A.L.T.: Alanine Transaminase; A.L.P.: Alkaline Phoapsatase. The present study observed no

significant adverse drug reaction after treatment. On case severity scale, mild adverse drug reactions were experienced and no patients were required to be admitted. Moreover, no need of any therapeutic changes or induction of additional therapy in patients was experienced during the study. The list of adverse events experiences has been listed in Table 4. Antiemetic and analgesics had to be prescribed for a few patients complaining of nausea and headache. All adverse events were observed to be sub-acute or latent in the beginning of the treatment but no acute onset were present within 60 minutes of treatment. The study exhibited that 24 patients experienced at least 1% undesirable events during treatment. All A.D.R.s were analyzed using Naranjo Algorithmic scale to find out the causal relationship between the drug and adverse event. On the basis of Naranjo A.D.R. Probability Scale, the cases of adverse incidences were considered as mild in severity (score 1-4) and in rest were doubtful (score=0).

Table 4: Adverse events (at least 1%in treatment group) frequently experienced by patients

Adverse Events Variables	Number	Percentage
Patient with ant A.E.s	24	42.1052
URTI	7	12.2807
Pneumonia	3	5.263158
Oral Candidiasis	1	1.754386
Cough	7	12.2807
Nausea	5	8.77193
Tremor	6	10.52632
Tachycardia	5	8.77193
Dryness of mouth	6	10.52632
Headache	4	7.017544

Total patients studies=57; A.E.: Adverse Events; URTI: Upper Respiratory Tract Infection.

Discussion

The present study was designed to assess the 4-week efficacy and safety of 'IND-GLY' in patients with mild to moderate asthma patients. The dual bronchodilator combining of indacaterol and glycopyrronium with a fixed dose of single administration per day has been approved for treatment of COPD [13, 14]. However, the role of combined indacaterol and glycopyrronium for treating bronchial asthma is not up to the scratch and is still under consideration. In most of the published articles 100-400 µg of indacaterol and 50 µg of glycopyrronium had been used either as mono-therapy or in combination with other drugs for treatment [9, 14, 18-21]. No fixed dose concentration of the drugs in combination has been decided yet for the treatment purpose [22]. Therefore, in the current investigation, the fixed dose combination of indacaterol (110 µg) and glycopyrronium (50 µg) inhaled once daily was used for treating bronchial asthma. FEV_1 is the standard criteria for assessing the effectiveness of inhaled therapies in asthma patients. This can be achieved by using spirometer. The process spirometry involves measurement of time, volume and air flow throughout inhalation and expiration [23, 24]. In the present study FEV_1 was considered as efficacy parameter to assess the combinatorial potential of indacaterol-glycopyrronium in patients of bronchial asthma. Improved FEV_1 of 7.78%, 8.37%, 7.82% and 6.9% was calculated on 3rd, 7th, 14th and 28th days post treatment respectively. The study asserted statistically significant improvement in FEV_1 on different days from baseline (p<

0.05). In the present study, FEV_1 at week 4 was 1.7577 ± 0.62 litres (Table 1). A comparative study by Dahl et al., 2013 reported FEV_1 at 4th week for combination of indacaterol (110µg) and glycopyrronium (50 µg) was 1.5±0.02 litres; whereas FEV_1 for combination of indacaterol (150µg) and glycopyrronium (50 µg) was 1.5±0.18 litre [22]. The active treatment may be attributed for sustainable improved lung function. In year 2013, Bateman et al. had reported a significant improvement in FEV_1 (+16%) dual drug therapy in comparison to mono-therapy of indacaterol and glycopyrronium throughout the study for 26 week [13]. Other comparative studies have also reported of improved FEV_1 giving better spirometric indices [14, 25-26].

Effectiveness of the 'IND-GLY' was further investigated by clinical improvement symptom score. The symptom score is actually a patient report outcome that summarises the occurrence of asthmatic symptoms like included dyspnoea, chest tightness, cough and their effect on daily activities and sleep [27]. A value between 0-5 was designated to each symptom. Higher the score value more is the severity of the disease [27]. The present study demonstrated that treatment with combination of indacaterol and glycopyrronium had improved symptom score with respect to baseline value among asthma patients (Figure 1). Collective score of the four parameters namely dyspnoea, chest stiffness, cough and night sleep was taken to evaluate the condition of the patient during each visit. Total symptom score on Day 1 was 8.89 which decreased to 6.61 on 28th day of treatment (Figure 1). Similar observations have been made in available literatures [7, 14, 22, 28-29]. The synergy between the two drugs may be attributed to their complementary mode of action [7, 22]. Glycopyrronium antagonizes acetylcholine effect and amplifies the relaxation of muscles of airway passage. Indacaterol further enhances muscle relaxation by activating ion channels and other intracellular signalling pathways [7, 22].

Laboratory tests and electrocardiography depicted no significant changes in comparison to baseline values. There was slight increase in pulse rate indicating increased heart rate. No remarkable variation was observed in systolic-diastolic blood pressure and haematological parameters with respect to the baseline values (Table 2-3). It is mandate to assess the safety parameters for any therapeutic study. Therefore, the incidence of the adverse events during the treatment was surveilled. No significant safety concern was evident from the study. On the scale of Niranjo algorithm, the adverse drug reactions were mild in severity which meant that there was no hospitalization, modification in therapy or additional treatment was provided. Cough and upper respiratory tract infection was the most common side effect followed by tremor and dryness of mouth (Table 4). Similar analysis was made by Wedzicha et al. [29]. β-agonist drugs with heavy doses often results in systemic absorption of part of drugs that leads to tremor response. Tremor is one of the most characteristic adverse effects following administration of β-adrenergic agonists. Dryness of mouth may be reasoned due to the anticholinergic effect of glycopyrronium. Similar observational pattern has been mentioned by other scientist [7, 22, 29].

Conclusion

The multi-analytical study reassured that administration of "IND-GLY' once per day improves lung function and symptom score and exhibited no safety issue. This dual drug therapy benefitted the patients of bronchial asthma in relieving from the chronic symptoms. Thus opening a path to be a tale of desirable hope and adding effective therapeutic armamentarium for the treatment of bronchial asthma.

Acknowledgments

The authors thank the patients who participated and the clinical center staff. The authors thank Aziz Writing Solutions for assisting in manuscript preparation and publication.

Funding

Any agencies did not fund the study.

Author contribution

All authors contributed to the concept and design of study and agree to be accountable for all aspect of this work. The authors contributed to the preparation of the manuscript draft, critical review and approval of manuscript for submission to the journal.

Trial registration number (T.R.N.): CTRI/2018/05/014079

References

1. Global Initiative for Asthma (2022) Global Strategy for Asthma Management and Prevention. Available from: www.ginasthma.org. Accessed 7 Oct 2022
2. Alomary SA, Al Madani AJ, Althagafi WA et al. (2022) Prevalence of asthma symptoms and associated risk factors among adults in Saudi Arabia: A national survey from Global Asthma Network Phase I. World Allergy Organization Journal 15(1):100623. doi: https://doi.org/10.1016/j.waojou.2021.100623
3. Lommatzsch M, Buhl R, Korn S (2020) The Treatment of Mild and Moderate Asthma in Adults. Dtsch Arztebl Int 117(25):434-44. doi: 10.3238/arztebl.2020.0434
4. World Health Organization (WHO) website (2022) Asthma. Available from: https://www.who.int/news-room/fact-sheets/detail/asthma. Accessed 7 Oct 2022
5. Sovani MP, Martin MJ (2022) Inhaled Corticosteroids for asthma treatment in India: An urgent and radical rethink needed. Lung India: Official organ of Indian Chest Society 39(4):311-312. doi: https://doi.org/10.4103/lungindia.lungindia_311_22
6. Singh D, Beier J, Astbury C et al. (2022) The novel bronchodilator navafenterol: a phase 2a, multicentre, randomised, double-blind, placebo-controlled crossover trial in COPD. Eur Respir J 59(4):2100972. doi: https://doi.org/10.1183/13993003.00972-2021
7. Oba Y, Keeney E, Ghatehorde N et al. (2018) Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis. Cochrane Database Syst Rev 12(12):Cd012620. doi: http://doi.org/10.1002/14651858.CD012620.pub2
8. Ni H, Moe S, Soe Z et al. (2018) Combined aclidinium bromide and long-acting beta2-agonist for chronic obstructive pulmonary disease (COPD). Cochrane Database Syst Rev 12(12):Cd011594. doi: http://doi.org/10.1002/14651858.CD011594.pub2
9. Feldman G, Siler T, Prasad N et al. (2010) Jack D, Piggott S, Owen R, et al. efficacy and safety of indacaterol 150 microg once-daily in COPD: a double-blind, randomised, 12-week study. B.M.C. pulmonary medicine 10:11.doi: http://doi.org/10.1186/1471-2466-10-11
10. Gosens R, Gross N (2018) The mode of action of anticholinergics in asthma. Eur Respir J, 52(4): 1701247. doi: http://doi.org/10.1183/13993003.01247-2017
11. Ohar JA, Bowling A, Goodin T et al. (2019) Efficacy and safety of glycopyrrolate in patients with COPD by reversibility: pooled analysis of GEM1 and GEM2 12-week studies. Int

J Chron Obstruct Pulmon Dis 14:461-470. doi: http://doi.org./10.2147/copd.s194102
12. Hsu E, Bajaj T (2022) Beta 2 Agonists. In: StatPearl. Treasure Island (F.L.): StatPearls Publishing. Available from: https://www.ncbi.nlm.nih.gov/books/NBK542249/ . Accessed 30 Sep 2022
13. Bateman ED, Ferguson GT, Barnes N et al. (2013) Dual bronchodilation with QVA149 versus single bronchodilator therapy: the SHINE study. Eur Respir J 42(6):1484-1494. doi: http://doi.org/10.1183/09031936.00200212
14. Horita N, Kaneko T (2015) Role of combined indacaterol and glycopyrronium bromide (QVA149) for the treatment of COPD in Japan. Int J Chron Obstruct Pulmon Dis 10(1):813-822. doi: https://doi.org/10.2147/COPD.S56067
15. Tashkin DP, Gross NJ (2018) Inhaled glycopyrrolate for the treatment of chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 13:1873-1888. doi: http://doi.org/10.2147/copd.s162646
16. Kadam P, Bhalerao S (2010) Sample size calculation. Int J Ayurveda Res 1(1): 55-57. doi: http://doi.org/10.4103/0974-7788.59946
17. Akram MF, Nasiruddin M, Ahmad Z et al. (2012) Doxofylline and theophylline: a comparative clinical study. J Clin Diagn Res 6(10):1681-1684. doi: http://doi.org/10.7860/jcdr/2012/4697.2643
18. Chapman KR, Rennard SI, Dogra A et al. (2011) Long-term safety and efficacy of indacaterol, a long-acting β_2-agonist, in subjects with COPD: a randomized, placebo-controlled study. Chest 140(1):68-75. doi: http://doi.org/10.1378/chest.10-1830
19. Seth HD, Sultan S, Gotfried MH (2013) Role of indacaterol, a once-daily bronchodilator, in chronic obstructive pulmonary disease. J Thorac Dis 5(6):806-814. doi: http://doi.org/10.3978/j.issn.2072-1439.2013.10.11
20. Horita N, Goto A, Shibata Y et al. (2017) Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus inhaled corticosteroid (I.C.S.) for stable chronic obstructive pulmonary disease (COPD). Cochrane Database Syst Rev 2(2):Cd012066. doi: http://doi.org/10.1002/14651858.CD012066.pub2
21. Beier J, Watz H, Diamant Z et al. (2021) Lung function improvements following inhaled indacaterol/glycopyrronium/mometasone furoate are independent of dosing time in asthma patients: a randomised trial. E.R.J. Open Res 7(2):00425-2020 doi: https://doi.org/10.1183/23120541.00425-2020
22. Dahl R, Jadayel D, Alagappan VK et al. (2013) Efficacy and safety of QVA149 compared to the concurrent administration of its monocomponents indacaterol and glycopyrronium: the BEACON study. Int J Chron Obstruct Pulmon Dis 8:501-508. doi: http://doi.org/10.2147/copd.s49615
23. Roychowdhury P, Badwal J, Alkhatib F et al. (2020) Spirometry Utilization Among Patients with Asthma. J Asthma Allergy 13:193-203. doi: http://doi.org/10.2147/jaa.s254431
24. Huang C, Izmailova ES, Jackson N et al., (2021) Remote FEV1 Monitoring in Asthma Patients: A Pilot Study Clin Transl Sci 14(2):529-35. doi: http://doi.org/10.1111/cts.12901
25. Chapman KR, Bateman ED, Chen H et al. (2015) QVA149 Improves Lung Function, Dyspnea, and Health Status Independent of Previously Prescribed Medications and COPD Severity: A Subgroup Analysis from the SHINE and ILLUMINATE Studies. Chronic Obstr Pulm Dis 2(1):48-60. doi:

http://doi.org/10.15326/jcopdf.2.1.2014.0140
26. Wedzicha JA, Banerji D, Chapman KR et al. (2016) Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD. N Engl J Med 374(23):2222-2234. doi: 10.1056/NEJMoa1516385
27. Clinical Review Report: Fluticasone Propionate (Aermony Respiclick): (Teva Canada Innovation) (2019) Indication: For the maintenance treatment of steroid-responsive bronchial asthma as prophylactic therapy in patients 12 years of age and older. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health. Available from: https://www.ncbi.nlm.nih.gov/books/NBK541829/. Accessed 01 Oct 2022
28. Mahler DA, Decramer M, D'Urzo A et al. (2014) Dual bronchodilation with QVA149 reduces patient-reported dyspnoea in COPD: the BLAZE study. Eur Respir J 43(6):1599-1609. doi: http://doi.org/10.1183/09031936.00124013
29. Wedzicha JA, Zhong N, Ichinose M et al. (2017) Indacaterol/glycopyrronium versus salmeterol/fluticasone in Asian patients with COPD at a high risk of exacerbations: results from the FLAME study. Int J Chron Obstruct Pulmon Dis 12:339-349. doi: http://doi.org/10.2147/copd.s125058.