Jerzy Kozielski

School of Medicine with the Division of Dentistry in Zabrze, Department of Lung Diseases and Tuberculosis, Medical University of Silesia in Katowice, Poland

Cardiovascular safety of two bronchodilators' fixed-dose combination: indacaterol and glycopyrronium

Bezpieczeństwo sercowo-naczyniowe preparatu złożonego z dwóch leków rozszerzających oskrzela: indakaterolu i glikopirronium

The author declares no financial disclosure

Abstract

Combination therapy with anticholinergics and β_2 -agonists should be used in COPD patients after failure of previous monotherapy with one of these drugs. Synergistic effect of both mechanisms of bronchodilation can maximize the efficacy of separately administered drugs. The effectiveness of the combination of LABA and LAMA is already confirmed, nevertheless the question about the safety profile of this therapy is still remaining, particularly with regard to the cardiovascular system. The paper discusses the overall safety profile of the combined preparation compare to placebo as well as the active comparators, especially the cardiovascular safety of fixed-dose formulation. Based on the data it has been demonstrated, that the combination of two ultra-long-acting bronchodilators with different complementary mechanisms of action increases the effectiveness of COPD therapy without affecting the safety.

Key words: combination therapy, indacaterol, glycopyrronium, cardiovascular safety

Pneumonol Alergol Pol 2015; 83: 164–170

Streszczenie

Skojarzone leczenie β_2 -mimetykami z cholinolitykami powinno być zastosowane u chorych na przewlekłą obturacyjną chorobę płuc (POChP) w przypadku braku złagodzenia objawów przy podaniu jednego z tych leków. Działanie poprzez dwa mechanizmy rozszerzania oskrzeli może bowiem zmaksymalizować efekt bronchodylatacyjny. Potwierdzona skuteczność terapii skojarzonej LABA i LAMA wywołuje pytanie o jej profil bezpieczeństwa, zwłaszcza w odniesieniu do wpływu na układ sercowo-naczyniowy. W pracy omówiono ogólny profil bezpieczeństwa stosowania tego skojarzonego preparatu, profil bezpieczeństwa w stosunku do placebo, a także w stosunku do aktywnych komparatorów. Szczegółowej analizie poddano profil bezpieczeństwa sercowo-naczyniowego tego dwuskładnikowego preparatu. Na podstawie zgromadzonych danych wykazano, że połączenie tych dwóch ultra-długodziałających leków rozszerzających oskrzela o różnych, uzupełniających się mechanizmach działania zwiększa skuteczność terapii POChP, nie wpływając jednocześnie na spadek jej bezpieczeństwa.

Słowa kluczowe: leczenie skojarzone, indakaterol, glikopirronium, układ sercowo-naczyniowy

Pneumonol Alergol Pol 2015; 83: 164–170

Address for correspondence: prof. dr hab. n. med. Jerzy Kozielski, Klinika Chorób Płuc i Gruźlicy SUM, ul. Ks. Koziółka 1, tel.: +48 32 373 22 35,

e-mail: ftpulmza@sum.edu.pl

DOI: 10.5603/PiAP.2015.0026

Received: 22.01.2015

Copyright © 2015 PTChP

ISSN 0867–7077

Introduction

As it was presented in *Global Initiative for Chronic Obstructive Lung Disease* (GOLD 2014) strategy, the combination therapy with anticholinergics and β_2 -agonists could be considered in COPD patients after failure of previous monotherapy with one of these drugs [1]. The combination of LABA (long-acting beta 2-agonist) and LAMA (long-acting muscarinic agonist) is very often suggested as an alternative therapy for patients in group B, C and D. Compare to the dose increasing during monotherapy, the combination of the bronchodilating drugs from two different classes could improve the effectiveness as well as decrease the risk of side-effects [2]. Additionally, two different mechanisms of bronchodilation can maximize this effect and equalize the diurnal variation in the intensity of symptoms, resulting from the higher daily activity of sympathetic system in contrary to the nocturnal activity of parasympathetic system. The 24-hour activity of the drug provides the effect of "pharmacological stent" of bronchial tree, leading to reducing of hyperinflation and subsequent alleviation of dyspnea, which is the most worrisome symptom reported by COPD patients.

The effectiveness of the combination of LABA and LAMA is already confirmed, nevertheless the question about the safety profile of this therapy is still remaining, particularly with regard to the cardiovascular system. The effects of action of beta-adrenoreceptor agonists (β -agonists) is relaxation of bronchial smooth muscle and in heart — increasing of sinus rhythm frequency (positive chronotropic effect), increasing of conduction velocity in atrioventricular (AV) node (positive dromotropic effect) and increasing of contraction strength of the myocardium (positive inotropic effect). The influence of β_2 -mimetics on glucose and potassium serum concentrations is also observed [3], and hypokalemia additionally exacerbates proarrhythmogenic effect. On the other hand, muscarinic receptor agonists decrease the cholinergic system tension therefore could cause tachycardia [4]. Whilst the dose of anticholinergics increases, the inhibition of M2 receptors' stimulation in AV node could potentiate this effect [5]. There are some reports in literature about increasing risk of myocardial infarctions in patients treated with LAMA [6].

It has been observed, that combination treatment with LABA (salmeterole or formoterole) [7] with LAMA (tiotropium) [6] increased the heart rate as well as elicited other cardiovascular symp-

toms. Nevertheless, the clinical trials' results did not indicate the risk of higher frequency or intensity of side-effects during combination therapy with tiotropium (administered once daily) and formoterole (1 or 2 times per day) compare with monotherapy with those drugs [8, 9]. There are limited data about safety profile of combination therapy with salmeterole and tiotropium [10].

QVA149 in the novel fixed-dose combination of indacaterol (LABA) and glycopyrronium (LAMA), with unknown safety profile, especially in reference to cardiovascular system. The effectiveness of both monocomponents, indacaterol (ultra-LABA) [11–15] and glycopyrronium (LAMA) [16, 17] has been previously confirmed in number of clinical trials, as well as their safety profile including cardiovascular action.

This is all the more significant, because the patients with COPD are usually in old age, with many comorbidities, very often involving the cardiovascular system [18].

General safety profile

The clinical trial IGNITE indicated, that this fixed-dose combination is characterized by favorable safety profile and tolerance, and total side-effects frequency was similar to placebo and active control groups [19].

In general this combined preparation was well tolerated in patients with moderate-to-severe COPD and majority of adverse events were of mild and moderate intensity. No deaths related to the therapy have been noted [20–24]. Based on metaanalysis it has been revealed, that one third of 1076 patients treating with this fixed-dose combination had at least 3 cardiovascular risk factors [25]. The frequency of severe cardiovascular side-effects in patients treated with combination therapy (1.8%) was similar to the tiotropium group (1.7%), but lower than in patient treating with other comparators (indacaterol, glycopyrronium, SFC: 2.3–3%) or placebo (2.6%). Angina pectoris, atrial fibrillation and ventricular and supraventricular extrasystoles were noted in 3 (0.3%), 3 (0.3%), 3 (0.3%) and 2 (0.2%) patients treated with QVA149 (a pre-marketing name for indacaterol/glycopyrronium fixed dose combination as of 8th July 2014), respectively [25]. The frequency of atrial fibrillation (both the first episodes and recurrent) was 0.8% in group treated with QVA149 and it was similar to the placebo group (0.6%), but lower as compare with patients treated with indacaterol (1.5%), glycopyrronium (2.1%), tiotropium (1.3%) and SFC (2.7%). The

changes of QTc length in ECG examination were noted in 1 patient taking QVA149. 1 in placebo group (in both cases it was QT prolongation) and in 2 patients treated with indacaterol (ventricular tachycardia) [25].

In general the fixed-dose combination of indacaterol/glycopyrronium (IND/GLY) was also well tolerated by patients with severe-to-very severe COPD with high risk of exacerbations [26]. The frequencies of particular cardiovascular abnormalities, such as: atrial fibrillation, myocardial infarction, cardiac arrest and heart failure were similar ($\leq 1\%$) to the groups taking glycopyrronium and tiotropium [26].

Safety profile of fixed-dose combination indacaterol/glycopyrronium versus placebo

General safety profile as well as profile of cardiovascular and cerebrovascular side-effects of QVA149 was similar to the placebo, both during 6 and 12 months observation in patients with moderate-to-severe COPD [22, 23].

In 26-weeks clinical trial SHINE the frequency of serious cardiovascular side-effects was comparable in group treated with IND/GLY and taking placebo (0% in IND/GLY group vs. $n = 1$, 0.4% in placebo group). Paroxysmal atrial fibrillation and atrial flutter were diagnosed in 2 (0.4%) patients treated with IND/GLY but in none in the placebo group. There were no clinically important differences between both groups regarding QTcF interval in ECG recording [23].

In 52-weeks clinical trial, investigating the safety of combination therapy with IND/GLY (ENLIGHTEN [22]), the cardiovascular and cerebrovascular (CCV) side-effects were reported in active treatment as well as placebo group in 5.3% and 2.7% patients, respectively. The severe CCV were confirmed in 5 patients taking IND/GLY (two patients had major adverse cardiovascular events [MACE] deemed as connected with the progression of previously existing disease; none of that events were noted in the placebo group). Ratio of MACE incidences per 100 patient-years was 1.0 in the group treated with IND/GLY and 0 in group taking placebo, and difference in frequency of CCV serious adverse event (SAE) between both groups did not reach statistical significance (odds ratio [OR] 3.25; $p = 0.284$).

Based on network metaanalysis including 1547 patients treated with combination therapy and 2141 taking placebo it has not been indicated the increased risk of death (hazard ratio, [HR] 0.922, 95% confidence interval [CI] 0.338, 2.511),

severe CCV events (HR 0.597, 95% CI 0.287, 1.241), MACE (HR 0.984, 95% CI 0.417, 2.319) or atrial fibrillation/flutter episodes (HR 1.017, 95% CI 0.479, 2.157) [27].

Side-effects of fixed-dose combination indacaterol/glycopyrronium versus active comparators

Side-effects profile of the fixed-dose combination was similar to the safety profiles of active comparators: monocomponents — IND/GLY, used separately or combined, as well as tiotropium and combination of salmeterol and fluticasone [21, 22, 24–26, 28].

In 4-weeks clinical trial BEACON, comparing efficacy and safety of fixed-dose combination IND/GLY with relevant monocomponents (IND and GLY) there were no CCV SAE reported in any of the groups [28].

Similarly, in SPARK clinical trial, involving patients with severe and very severe COPD, there was no increasing number of side-effects, including MACE in patients treated with fixed-dose combination IND/GLY compare with glycopyrronium and tiotropium [26]. Serious adverse events, cardiovascular serious adverse events and MACE were noted in 23, 3.7 and 1.4% patients treated with combination therapy, 24, 3.4 and 2.0% patients treated with glycopyrronium and 22, 3.5 and 1.1% patients taking tiotropium, respectively.

In 26-weeks clinical trial assessing efficacy and safety of combination therapy (SHINE) [23] there were not reported serious CCV events in actively treated group as compare with isolated cases in the groups treated with indacaterol, glycopyrronium or tiotropium. Furthermore, there were no clinically important differences between the groups according to QTc interval (Fridericia's formula).

In 26-weeks clinical trial ILLUMINATE the frequency of cardiovascular abnormalities leading to treatment interruption was the same (0.8%) in the group of patients treated with fixed-dose combination IND/GLY and taking combination of salmeterole and fluticasone (SFC 50/500 mcg). One patient in SFC group died during trial, and a sudden cardiovascular death was recognized as a cause [21]. There were no new safety signals in metaanalyses involving patients with moderate-to-severe COPD treated with fixed-dose combination IND/GLY as compare with active comparators: indacaterol, glycopyrronium, tiotropium and salmeterole/fluticasone [24]. The frequency of adverse events and serious adverse events including progression of COPD were

similar or even lower in patients treated with fixed-dose combination IND/GLY as compared with active comparators [24]. Additionally, no increased risk of CCV was observed in this group. The frequency of CCV, including SAE (also MACE) and atrial fibrillation/flutter episodes in patients treated with combination therapy IND/GLY was similar or numerally lower versus active comparators [24, 25].

Cardiovascular safety profile of fixed-dose combination indacaterol/glycopyrronium

As the results of the searching of PubMed literature database (using search terms: „QVA149 + cardiac safety”, „QVA149+ cardiovascular”, „QVA149+potassium” 4 publications describing QVA149 cardiovascular safety profile, of which 2 were rejected due to secondary character or lack of direct relevance with treatment of that preparation. One of those trials involved healthy volunteers [29], and the second one patients with moderate-to-severe COPD [30].

The first trial it was randomized, double-blinded study, assessing effect of fixed-dose combination on cardiovascular parameters and glucose and potassium serum concentration in 50 healthy volunteers compare to placebo [29]. Similar analyses were performed versus indacaterol 600 µg, glycopyrronium 200 µg and salmeterole 200 µg. Although the doses of the combination therapy exceeded 4-fold the therapeutic doses (indacaterol 440 µg and glycopyrronium 200 µg), no clinically important effect on cardiovascular parameters e.g. heart rate or QTcF interval prolongation in ECG was indicated. The biggest change of heart rate at some time point was 5.69 beats per minute (90% CI: 2.71; 8.66). Slight decreasing of heart rate was observed in the group of patients treated with fixed-dose combination as compare to indacaterol and salmeterole, but little increasing (by 1.78 beats per minute) versus glycopyrronium (Fig. 1). Similarly, there was no important effect on the length of QTcF interval in ECG recording comparing to other active therapies. Changing of potassium serum concentration compare to placebo and glycopyrronium was small. During both therapies the biggest changes of potassium serum concentration were observed 4 hours 10 minutes after dose administration by -0.14 mmol/l (90% CI: -0.26 , -0.01) and -0.12 mmol/l (90% CI: -0.25 , 0.01), respectively. In the majority of time points the changes of potassium serum concentration in patients treated with combination therapy were smaller than in patient

Figure 1. Mean changes in heart rate compared with the baseline for 24h; bpm — beats per minute

taking salmeterole, and the biggest difference was 0.21 mmol/l (90% CI: 0.08, 0.34 mmol/l) at 2 hours 10 minutes after dose administration. The biggest differences in glucose serum concentration in the group of patients treated with QVA149 compare to placebo and glycopyrronium were 0.67 mmol/l (90% CI: 0.30, 1.03) and 1.13 mmol/l (90% CI: 0.77, 1.49) at 8 hours 10 minutes and at 6 hours 10 minutes after dose administration, respectively. Comparing to indacaterol the differences of glycaemia were smaller, with the maximum of -0.18 mmol/l (90% CI: -0.54 , 0.18) at 6 hours 10 minutes after dose administration. The biggest difference was observed comparing to salmeterole e.g. -1.19 mmol/l (90% CI: -1.56 , -0.82) at 6 hours 10 minutes after dose administration.

The safety profiles of all analyzed therapies were similar, no serious adverse events and deaths were reported. The majority of adverse events were of mild intensity, the only moderate adverse event was the headache in one patients treated with fixed-dose combination of indacaterol and glycopyrronium. The authors concluded, that combination therapy did not induce tachycardia comparing to indacaterol and glycopyrronium alone and did not influence QTcF interval in

healthy volunteers. As compared to salmeterole, effect on heart rate and QTcF interval was smaller. No clinically important changes of potassium and glucose serum concentrations were noted. In general, the combination therapy was well tolerated.

Double-blinded, placebo-controlled clinical trial with parallel groups assessed cardiovascular safety of subtherapeutic doses of combination therapy (600/100 μ g, 300/100 μ g or 150/100 μ g) and indacaterol alone in therapeutic dose of 300 μ g versus placebo in 257 patients with moderate-to-severe COPD. The endpoints included effects on 24-hours heart rate measured in Day 14 [30] and change of baseline mean daily heart rate in Day 1 and 14, as well as changes of QTcF interval in ECG recording (Fridericia's formula) in Day 14. No statistically significant changes of mean daily heart rate were observed in any of the patients treated with different doses of combination therapy and indacaterol alone 300 μ g. For 98.3% of differences versus placebo CIs ranged from -5 to $+5$ beats per minute. Similar analyses in Day 1 revealed, that mean daily heart rate in all therapeutic arms tended to decrease, with the biggest change of baseline values in patients treated with QVA149 600/100 μ g (least mean squares -2.877 beats per minute as compare with -2.770 , -0.547 , -1.849 , and -0.329 beats per minutes for QVA149 300/100 μ g, QVA149 150/100 μ g, indacaterol 300 μ g, and placebo, respectively. The differences for two highest doses of QVA149 versus placebo were very close, but did not reach the statistical significance ($p = 0.05$).

No cases of ventricular tachycardia, ventricular fibrillation/flutter or *torsades de pointes* were observed. In the group of patients treated with the dose of combination therapy of 150/100 μ g, with the more frequent baseline sporadic tachycardia (14.3%) and arrhythmias, no tendency neither to increasing or decreasing of those changes nor differences between therapeutic groups were noted. There were few episodes of atrial flutter, but the mean values in all analyzed groups, as well as during all study were zero. The frequency of short-lasting episodes of nonfixed supraventricular tachycardia was the highest in the group treated with QVA149 150/100 μ g, but percentage value recovered to the baseline in Day 14. No differences of these episodes changes were noted in any of the therapeutic groups; the supraventricular arrhythmias slightly changed between the groups.

QTc intervals were similar in all time points (normal value < 470 ms in women and < 450 ms in men). No clinically important differences in mean QTc intervals (Fridericia's formula) be-

tween groups were noted. Visible changes of QTc interval were most frequent in group of patients treated with fixed-dose combination 600/100 μ g (12.2%) as compare to lower doses of 300/100 μ g (7.8%) and 150/100 μ g (2.0%); no changes of baseline values did not exceeded the threshold > 60 ms. In any woman QTc interval did not reach the value > 470 ms, and maximum prolongation of baseline QTc interval was below 30 ms using Fridericia's formula. According to LS of QTc interval the differences between groups were minimal and no relations with administered dose was observed.

The tendency to shortening of baseline QTc interval (< 10 ms) was observed in all but indacaterol/glycopyrronium 150/100 therapeutic groups. In this group the prolongation of QTc interval was noted in Day 7 and 14, nevertheless the values before dose administration were lower than baseline, and changes after taking a dose were small.

In general the frequency of clinical symptoms was similar in all therapeutic groups. There was a tendency to decreasing of heart rate and blood pressure (both diastolic and systolic) after dose administration, without clinical importance. In all groups with active treatment the decreasing of heart rate after dose inhalation was noted in Day 1, 7 and 14 with mean values ranged from 1.0 to 5.0 beats per minute. The mean change was bigger in patients treated with QVA149 as compare to indacaterol alone 300 μ g, although no relations between dose and response were noted.

In all investigated groups the changes from baseline values of mean sitting diastolic blood pressure (msDBP) decreased. Decreasing of msDBP values in Day 1, 7, and 14 was detectable, but did not exceed 4 mm Hg, what was of no clinical importance.

Majority of side-effects were of mild and moderate intensity. No relationship between dose of combination therapy and frequency of side-effects was noted. Serious adverse events were reported in 5 (2%) patients, leading in 3 (1.2%) of them to dose interruption. The following adverse events were deemed as related to study drug administration: ventricular tachycardia ($n = 1$ [2.0%]; combination therapy 150/100 μ g), atrial fibrillation ($n = 1$ [2.0%]; combination therapy 600/100 μ g) and hyperkalemia ($n = 1$ [2.0%]; combination therapy 600/100 μ g). Mentioned cardiovascular events were revealed based on Holter ECG recording, but without clinical symptoms. Serious adverse events not related to the study drug included: anemia ($n = 1$ [2.0%]; combination

therapy 150/100 μ g) and COPD exacerbation ($n = 1$ [1.9%]; placebo).

Summary

Combination of two bronchodilating drugs of different, complementary mechanisms of action improve the efficacy of COPD treatment, without reducing of safety. Combined preparation of indacaterol and glycopyrronium (Ultibro Breezhaler 110/50 μ g) is a fixed-dose combination of LABA and LAMA, administered once daily, with additional therapeutic benefits for COPD patients and favorable safety profile. Efficacy of that drug was confirmed in many clinical trials based on spirometric parameters as well as clinical symptoms, especially dyspnea, general state of health, exercise tolerance, COPD exacerbation rate and usage of rescue medications.

The long-lasting, 24-hours bronchodilating effect of the drug provides „pharmacologic stent” for airways, leading to reducing of hyperinflation and subsequently to alleviating dyspnea. Additionally, it has beneficial influence on cardiovascular system. Hyperinflation decreases blood volume in chest and causes insufficient left ventricular filling. It has been noted, that IC/TLC (inspiratory capacity to total lung capacity ratio, index of lung hyperinflation) $< 0,25$ leads to disturbances of left ventricular diastolic filling [31]. It was additionally confirmed, that this measure correlates with left ventricle end-diastolic dimension (LVEDD). Diastolic dysfunction of left ventricle is independent factor affecting exercise tolerance in COPD patients. No clinical trials were identified directly investigating the influence of bronchodilating therapy on cardiovascular parameters as follow: ventricular dimension, ejection fraction (EF) and parameters of left ventricular filling. It could be assumed, that decreasing of hyperinflation (based on IC measurement) by using combination therapy with ultra-long acting drugs e.g. indacaterol and glycopyrronium (BRIGHT study [32]) should translate into improvement of circulation parameters and subsequent improvement of exercise tolerance. It is already proved, that bronchodilating drugs, together with lung volume reduction surgery (LVRS) and pulmonary rehabilitation contribute to improvement of cardiovascular hemodynamic parameters [33].

Combination of two drugs in one capsule confirmed also the favorable safety profile, including cardiovascular safety both in healthy volunteers and patients with COPD. Once daily

administration improve patients' adherence, leading to improved treatment efficacy. According to described features, presented fixed-dose combination is a valuable therapeutic option for patients on different stages of COPD.

Conflicts of interest

The author declares no conflict of interest.

References

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of COPD. Updated February 2014. www.goldcopd.org.
2. Vogelmeier C, Kardos P, Harari S, Gans S.J, Stenglein S, Thirlwell J. Formoterol mono- and combination therapy with tiotropium in patients with COPD: a 6-month study. *Respir Med* 2008; 102: 1511–1520. doi: 10.1016/j.rmed.2008.07.020.
3. Bremner P, Woodman K, Burgess C. et al. Comparison of the cardiovascular and metabolic effects of formoterol, salbutamol and fenoterol. *Eur Respir J* 1993; 6: 204–210.
4. Ray NC, Alcaraz L. Muscarinic antagonist- β 2-adrenergic agonist dual pharmacology molecules as bronchodilators: a patent review. *Expert Opin Ther Pat* 2009; 19: 1–12, doi: 10.1517/13543770802630331.
5. Sarria B, Naline E, Zhang Y. et al. Muscarinic M2 receptors in acetylcholine-isoproterenol functional antagonism in human isolated bronchus. *Am J Physiol Lung Cell Mol Physiol* 2002; 283: L1125–L1132.
6. Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and metaanalysis. *JAMA* 2008; 300: 1439–1450. doi: 10.1001/jama.300.12.1439.
7. Salpeter SR, Ormiston TM, Salpeter EE. Cardiovascular effects of β 2-agonists in patients with asthma and COPD: a meta-analysis. *Chest* 2004; 125: 2309–2321.
8. van Noord JA, Aumann JL, Janssens E. et al. Comparison of tiotropium once daily, formoterol twice daily and both combined once daily in patients with COPD. *Eur. Respir. J.* 2005; 26: 214–222.
9. van Noord JA, Aumann JL, Janssens E. et al. Effects of tiotropium with and without formoterol on airflow obstruction and resting hyperinflation in patients with COPD. *Chest* 2006; 129: 509–517.
10. Cazzola M, Santus P, Verga M, Mondoni M, Di Marco F, Matera MG. The functional impact of adding salmeterol to tiotropium in patients with stable COPD. *Respir Med* 2004; 98: 1214–1221.
11. Rennard S, Bantje T, Centanni S. et al. A dose-ranging study of indacaterol in obstructive airways disease, with a tiotropium comparison. *Respir Med* 2008; 102: 1033–1044. doi: 10.1016/j.rmed.2008.02.001.
12. Beier J, Chané P, Martinot JB. et al. Safety, tolerability and efficacy of indacaterol, a novel once-daily β 2-agonist, in patients with COPD: A28-day randomised, placebo controlled clinical trial. *Pulm Pharmacol Ther* 2007; 20: 740–749.
13. Dahl RP, Chung KF, Buhl R. et al. Efficacy of a new once-daily long-acting inhaled β 2-agonist indacaterol versus twice-daily formoterol in COPD. *Thorax* 2010; 65: 473–479. doi: 10.1136/thx.2009.125435.
14. Donohue JF, Fogarty C, Lötvall J. et al. Once-daily bronchodilators for chronic obstructive pulmonary disease: indacaterol versus tiotropium. *Am J Respir Crit Care. Med.* 2010; 182:155–162. doi: 10.1164/rccm.200910-1500OC.
15. Khindri S, Sabo R, Harris S, Jennings S, Drollman AF. Cardiac safety of indacaterol — no clinical effect on QT in healthy subjects. *Eur Respir J* 2009; 34 (Suppl. 53): 2031.
16. Vogelmeier C, Verkindre C, Cheung D. et al. Safety and tolerability of NVA237, a once-daily long-acting muscarinic antagonist, in COPD patients. *Pulm Pharmacol Ther* 2010; 23: 438–444. doi: 10.1016/j.pupt.2010.04.005.

17. Verkindre C, Fukuchi Y, Flémale A. et al. Sustained 24-h efficacy of NVA237, a once daily long-acting muscarinic antagonist, in COPD patients. *Respir Med* 2010; 104: 1482–1489. doi: 10.1016/j.rmed.2010.04.006.
18. Batura-Gabryel H, Grabicki M. Przewlekła obturacyjna choroba płuc i choroby sercowo-naczyniowe — „kontinuum sercowo-płucne”. *Pneumonol Alergol Pol* 2014; 82: 590–596.
19. Frampton JE. QVA149 (indacaterol/glycopyrronium fixed-dose combination): a review of its use in patients with chronic obstructive pulmonary disease. *Drugs* 2014; 74: 465–488. doi: 10.1007/s40265-014-0194-8.
20. Asai K, Minakata Y, Hirata K. et al. Once-daily QVA149 is safe and well tolerated and improves lung function and health status in Japanese patients with COPD: the ARISE study. *Eur Respir J* 2013; 42 (Suppl. 57): P3392.
21. Vogelmeier CF, Bateman ED, Pallante J. et al. Efficacy and safety of once-daily QVA149 compared with twice-daily salmeterol-fluticasone in patients with chronic obstructive pulmonary disease (ILLUMINATE): a randomised, double-blind, parallel group study. *Lancet Respir Med* 2013; 1: 51–60. doi: 10.1016/S2213-2600(12)70052-8.
22. Dahl R, Chapman KR, Rudolf M. et al. Safety and efficacy of dual bronchodilation with QVA149 in COPD patients: the ENLIGHTEN study. *Respir Med* 2013; 107: 1558–1567. doi: 10.1016/j.rmed.2013.05.016.
23. Bateman ED, Ferguson GT, Barnes N. et al. Dual bronchodilation with QVA149 versus single bronchodilator therapy: the SHINE study. *Eur Respir J* 2013; 42: 1484–1494. doi: 10.1183/09031936.00200212.
24. Welte T, Vogelmeier C, Dahl R. et al. Once-daily QVA149 has a good safety profile in patients with COPD. *Eur. Respir. J.* 2013; 42 (Suppl. 57): P757.
25. Ferguson GT, Barnes N, Mehta R. et al. Cardio- and cerebrovascular safety of QVA149: results from a pooled analysis. *Eur Respir J* 2013; 42 (Suppl. 57): P4139.
26. Wedzicha JA, Decramer M, Ficker JH. et al. Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study. *Lancet Respir Med* 2013; 1: 199–209. doi: 10.1016/S2213-2600(13)70052-3.
27. Chen H, D’Andrea P, Banerji D. QVA149 does not increase the risk of cardio- and cerebrovascular events, pneumonia and exacerbation events compared with placebo: a network meta-analysis across multiple safety databases. *Eur Respir J* 2013; 42 (Suppl. 57): P3638.
28. Dahl R, Jadayel D, Alagappan VK, Chen H, Banerji D. 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* 2013; 8: 501–508. doi: 10.2147/COPD.S49615.
29. Drollmann A, Brown M, Sechaud R. et al. Effect of dual bronchodilation with QVA149 on cardiac safety in healthy volunteers. *Int J Clin Pharmacol Ther* 2014; 52: 369–380. doi: 10.5414/CP202034.
30. Van de Maele B, Fabbri LM, Martin C, Horton R, Dolker M, Overend T. Cardiovascular safety of QVA149 a combination of indacaterol and NVA237 in COPD patients. *COPD* 2010; 7: 418–427. doi: 10.3109/15412555.2010.528812.
31. Watz H, Waschki B, Meyer T. et al. H. Decreasing cardiac chamber sizes and associated heart dysfunction in COPD: role of hyperinflation *Chest* 2010; 138: 32–38. doi: 10.1378/chest.09-2810.
32. Beeh KM, Korn S, Beier J. et al. Effect of QVA149 on lung volumes and exercise tolerance in COPD patients: The BRIGHT study. *Respir Med* 2014; 108: 584–592. doi: 10.1016/j.rmed.2014.01.006.
33. Visca D, Aiello M, Chetta A. Cardiovascular function in pulmonary emphysema. *Biomed Res Int* 2013; 2013: 184678. doi: 10.1155/2013/184678.