Dual-combination maintenance inhaler preferences in asthma and chronic obstructive pulmonary disease

Tervonen, Tommi; Martinez, Fernando J.; Hanania, Nicola A.; Heidenreich, Sebastian; Eudicone, James M.; Gilbert, Ileen

Published in:
Respiratory Medicine

DOI:
10.1016/j.rmed.2020.106278

Publication date:
2021

Respiratory Medicine 176 (2021) 106278

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: http://www.elsevier.com/locate/rmed

Dual-combination maintenance inhaler preferences in asthma and chronic obstructive pulmonary disease: A patient-centered benefit-risk assessment

Tommi Tervonen [a,b,*], Fernando J. Martinez [c], Nicola A. Hanania [d], Sebastian Heidenreich [a], James M. Eudicone [e], Ileen Gilbert [e]

[a] Patient-Centered Research, Evidera, London, UK
[b] Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands
[c] Pulmonary and Critical Care Medicine, Weill Cornell Medicine, New York, NY, USA
[d] Section of Pulmonary and Critical Care Medicine, Baylor College of Medicine, Houston, TX, USA
[e] Medical Affairs-Respiratory, AstraZeneca, Wilmington, DE, USA

ARTICLE INFO

Previous presentation: The results in this article were presented in part at the Annual Chest Meeting in New Orleans, LA, USA, October 19–23, 2019.

Keywords:
Asthma
COPD
Patient preferences
Benefit-risk assessment

ABSTRACT

Background: A variety of dual-combination maintenance inhalers are used to treat asthma and chronic obstructive pulmonary disease (COPD). Understanding patient preferences for treatment attributes may help select an optimal treatment from the patient perspective.
Methods: Patient preferences for maintenance inhaler device and medication attributes were elicited through a discrete choice experiment and used in benefit-risk assessments to calculate predicted choice probabilities (PrCPs) for 14 dual-combination maintenance inhalers in four treatment classes: lower- and higher-dose inhaled corticosteroid (ICS)/long-acting beta agonist (LABA) inhalers for asthma, and ICS/LABA and long-acting muscarinic antagonist (LAMA)/LABA inhalers for COPD.
Results: For all treatment classes, reduced exacerbations and faster onset of action were the most important attributes. For all classes, patients were willing to tolerate an extra yearly exacerbation to decrease the medication's onset of action from 30 to 5 min. For patients with asthma using lower-dose ICS/LABA (n = 497), budesonide/formoterol fumarate dihydrate (80 μg/4.5 μg) pressurized metered-dose inhaler (pMDI) had the highest PrCP (28.4%), and for those using a higher-dose ICS/LABA (n = 285), PrCPs were highest for mometasone furoate/formoterol fumarate dihydrate (200 μg/5 μg) pMDI (27.0%) and budesonide/formoterol fumarate dihydrate (160 μg/4.5 μg) pMDI (26.9%). For patients with COPD using an ICS/LABA (n = 574), budesonide/formoterol fumarate dihydrate (160 μg/4.5 μg) pMDI had the highest PrCP (56.6%), and for those using a LAMA/LABA inhaler (n = 217), tiotropium/olodaterol (2.5 μg/2.5 μg) soft mist inhaler had the highest PrCP (42.3%).
Conclusions: Patient preference data for maintenance inhaler attributes can be used to identify a preference order of inhalers in different treatment classes.

1. Introduction

A variety of inhaled fixed-dose dual-combination maintenance therapies are available for treating asthma and chronic obstructive pulmonary disease (COPD). These include inhaled corticosteroid (ICS)/long-acting beta agonist (LABA) inhalers for patients with asthma, and ICS/LABA and long-acting muscarinic antagonist (LAMA)/LABA inhalers for patients with COPD [1,2]. Understanding how patients value differences in efficacy, safety, and convenience attributes of the various maintenance inhalers can help clinicians determine the most appropriate treatment for their patients.

Quantitative methods for assessing preferences, such as discrete choice experiments (DCEs), can provide information about the trade-offs that patients are willing to make among treatment attributes [3]. We performed a DCE using a self-completed web-based questionnaire to elicit preferences of patients with asthma or COPD for inhaler device and medication attributes [4]. Attributes were selected based on patient focus groups [5], coupled with a literature review and expert clinical advice, to ensure that the DCE captured the patient perspective and was clinically relevant. The DCE revealed that the most important

* Corresponding author. Evidera, The Ark, 201 Talgarth Rd, London, W6 8DL, UK.
E-mail address: tommi.tervonen@evidera.com (T. Tervonen).

https://doi.org/10.1016/j.rmed.2020.106278
Received 18 May 2020; Received in revised form 9 September 2020; Accepted 27 November 2020
Available online 29 November 2020

Table 1
Attributes and levels assessed in the discrete choice experiment.

Attribute class	Attribute	Levels
Efficacy	Exacerbations per year	1, 2, 3[a]
	Onset of action (min)	5, 15, 20, 30[a]
Safety	5-year risk of osteoporosis	4%, 5%, 6%[a]
	5-year risk of pneumonia (COPD only)	10%, 15%, 20%[a]
Convenience	Dosing frequency	QD, BID[a]
	Priming	1 or 2 simple steps, discharge + 1 step, new canister + 1 step, new capsule each time[a]
	Inhaler device type	Pressurized, soft mist, dry powder[a]
	Dose counter	Every dose, every 10 doses, metered[a]

Abbreviations: BID, twice daily; COPD, chronic obstructive pulmonary disease; QD, once daily.
[a] Reference level.

maintenance inhaler attributes for patients with asthma and COPD were a rapid onset of symptom relief and a lower rate of exacerbations, although the safety of ICS and device and dosing attributes were also important [4].

In the current study, we analyzed the DCE results separately for patients with asthma using lower- and higher-dose ICS/LABA inhalers and for patients with COPD using ICS/LABA and LAMA/LABA inhalers. We then performed a benefit-risk assessment based on the DCE results to rank currently available dual-combination maintenance inhalers approved in the United States for treating asthma or COPD.

2. Materials and methods

2.1. Study design

This was a benefit-risk assessment in which elicited preferences from a DCE were used to rank dual-combination maintenance inhalers according to probabilities that patients would choose one inhaler over the other if given the choice. Two DCEs elicited preferences for seven (asthma) or eight (COPD) maintenance inhaler attributes in three domains: efficacy (onset of action and exacerbations per year), safety (5-year risk of osteoporosis and, for COPD, 5-year risk of pneumonia), and non-clinical features (device type, dosing frequency, dose counters, and priming) (Table 1). Each attribute included three levels selected based on asthma and COPD treatment product characteristics, feedback from clinical experts, and a review of clinical data sources, published studies on patient perceptions, and preference studies. The estimated preferences for maintenance inhaler attributes based on the DCE are reported elsewhere [4]. Advarra Institutional Review Board (Columbia, MD, USA) granted exemption from institutional review board oversight based on Department of Health and Human Services regulations.

2.2. Participants

The DCE included patients living in the United States with self-reported asthma or COPD. Patients with asthma had to be aged ≥18 years and have been using an ICS/LABA inhaler for ≥12 weeks. Patients with COPD had to be aged ≥40 years, be current or past smokers with a ≥10 pack-year history, using a maintenance inhaler to treat COPD for ≥12 weeks, and symptomatic (COPD Assessment Test™ [CAT] score >10) or had experienced ≥2 exacerbations or ≥1 COPD-related hospitalization in the past 12 months. Patients were excluded if they had asthma-COPD overlap syndrome or were receiving triple therapy (i.e., ICS/LABA + LAMA or ICS + LABA/LAMA) because fixed-dose triple combination therapies were not available in the United States when the study was conducted. All patients were required to provide informed consent.

2.3. Benefit-risk assessment and other statistical analyses

Elicited preferences for attributes from the DCE were used in a benefit-risk assessment that ranked maintenance inhalers based on predicted choice probabilities. The predicted choice probability describes the estimated proportion of patients expected to choose one inhaler over another, given the choice. Separate analyses were conducted for each of the following subgroups of patients: lower-dose ICS/LABA for asthma, higher-dose ICS/LABA for asthma, ICS/LABA for COPD, and LAMA/LABA for COPD.

Within each analysis, the value of alternative maintenance inhalers was assessed relative to a reference-level inhaler, which was a hypothetical inhaler with the least desirable level of performance on all attributes (e.g., a 30-min onset time, 6% five-year risk of osteoporosis, and twice-daily dosing). Maintenance inhaler performance estimate values are summarized in Table 2, sources for onset of action described in Supplemental Methods, and the performance calculations are shown in Supplemental Tables 1–3.

In each analysis, a multinomial logit model was estimated for the corresponding subgroup of patients. The models included linear coding for pneumonia, osteoporosis, and onset of action attributes to enable estimation of standard errors for the predicted treatment choice probabilities. Exacerbations were also linearly coded to allow the treatment value to be expressed as exacerbation equivalents. All other attributes were dummy coded. For linearized attributes, the coefficient indicated the utility that would be gained in reducing the attribute by one unit (e.g., a 1% reduction in five-year risk of osteoporosis, a 1-min decrease in onset time, or one less exacerbation). For attributes that were dummy coded, the utility effects for deviations from the reference level were estimated. The utility gained for the improvement in an attribute was divided by the utility gained for exacerbation reduction to obtain the maximum acceptable average increase in yearly exacerbations that patients would be willing to tolerate to obtain the improvements in the attribute. In each analysis, the overall value of each inhaler was obtained by summing the utilities (in exacerbation equivalents) for each attribute. Predicted choice probabilities were estimated from the total utilities using a logit model, and their standard errors for were estimated using a parametric bootstrap method.

Patient demographic and clinical characteristics were compared between treatment classes for asthma and COPD by analysis of variance for continuous variables and Chi-square test for categorical variables.

All statistical tests were two-sided and used a significance level of 0.05. Statistical analyses were performed using R version 3.4 (R Foundation for Statistical Computing, Vienna, Austria), MATLAB version R2017b (MathWorks, Natick, MA, USA), and Excel 365 ProPlus (Microsoft, Redmond, WA, USA).

3. Results

The DCE was completed by 810 patients with asthma and 1147 patients with COPD between May 30 and October 1, 2018. The current benefit-risk analysis was limited to patients with asthma using a lower-dose ICS/LABA inhaler (n = 497) or a higher-dose ICS/LABA inhaler (n = 285), and patients with COPD using a LAMA/LABA inhaler (n = 217) or an ICS/LABA inhaler (n = 497). Patients who reported using inhalers in different treatment classes were excluded from the analysis.

3.1. Participants

In all four treatment classes, approximately 60% of patients included in the analysis were female (Table 3). For patients with asthma, only racial background differed between inhaler classes: fewer patients on higher-dose ICS/LABA (71.9%) than on lower-dose ICS/LABA (79.9%) were white. For patients with COPD, those using a LAMA/LABA inhaler

Table 2
Performance of dual-combination maintenance inhalers.

Class/generic name	Trade name	Inhaler	Dose (μg)	Onset of action (min)[a]	5-year risk of osteoporosis (%)[b]	5-year risk of pneumonia (%)[c]	Dosing frequency	Priming	Inhaler device type	Dose counter
Asthma lower-dose ICS/LABA										
Budesonide/formoterol	Symbicort®	pMDI	80/4.5	15	4.7	N/A	BID	Discharge test doses on 1st use; 1 simple step	pMDI	Every 10 doses
Fluticasone propionate/ salmeterol	Advair®	Diskus®	250/50	30	5.2	N/A	BID	1-2 simple steps	DPI	Every dose
Fluticasone propionate/ salmeterol	Advair®	HFA	115/21	30	5.2	N/A	BID	Discharge test doses on 1st use; 1 simple step	pMDI	Every dose
Mometasone/formoterol	Dulera®	pMDI	100/5	15	5.2	N/A	BID	Discharge test doses on 1st use; 1 simple step	pMDI	Every dose
Fluticasone furoate/ vilanterol	Breo®	Ellipta®	100/25	15	5.2	N/A	QD	1 to 2 simple steps	DPI	Every dose
Asthma higher-dose ICS/LABA										
Budesonide/formoterol	Symbicort®	pMDI	160/4.5	15	4.7	N/A	BID	Discharge test doses on 1st use; 1 simple step	pMDI	Every 10 doses
Fluticasone propionate/ salmeterol	Advair®	Diskus®	500/50	30	5.4	N/A	BID	1 to 2 simple steps	DPI	Every dose
Fluticasone propionate/ salmeterol	Advair®	HFA	230/21	30	5.2	N/A	BID	Discharge test doses on 1st use; 1 simple step	pMDI	Every dose
Mometasone/formoterol	Dulera®	pMDI	200/5	15	5.2	N/A	BID	Discharge test doses on 1st use; 1 simple step	pMDI	Every dose
Fluticasone furoate/ vilanterol	Breo®	Ellipta®	200/25	15	5.4	N/A	QD	1 to 2 simple steps	DPI	Every dose
COPD ICS/LABA										
Budesonide/formoterol	Symbicort®	pMDI	160/4.5	5	4.7	11.5	BID	Discharge test doses on 1st use; 1 simple step	pMDI	Every 10 doses
Fluticasone propionate/ salmeterol	Advair®	Diskus®	250/50	19	5.2	17.4	BID	1 to 2 simple steps	DPI	Every dose
Fluticasone furoate/ vilanterol	Breo®	Ellipta®	100/25	16	5.2	17.4	QD	1 to 2 simple steps	DPI	Every dose
COPD LAMA/LABA										
Glycopyrrolate/formoterol	Bevespi®	Aerosphere®	18/9.6	5	N/A	N/A	BID	Discharge test doses on 1st use; 1 simple step	pMDI	Every 10 doses
Tiotropium/olodaterol	Stiolto®	Respimat®	2.5/2.5	5	N/A	N/A	QD	Insert canister on 1st use; 2 steps	Soft mist	Metered
Glycopyrrolate/ indacaterol	Utibron®	Neohaler®	27.5/ 15.6	5	N/A	N/A	BID	Insert new capsule each time	DPI	Every dose
Umeclidium/vilanterol	Anoro®	Ellipta®	62.5/25	27	N/A	N/A	QD	1 to 2 simple steps	DPI	Every dose

Treatments within a single class were assumed to have the same reduction of yearly exacerbations. Abbreviations: BID, twice daily; DPI, dry powder inhaler; HFA, hydrofluoroalkane; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; N/A, not applicable; pMDI, pressurized metered-dose inhaler; QD, once daily.

[a] Sources provided in Supplemental Table 1.

[b] Calculations and sources described in Supplemental Table 2.

[c] Calculations and sources provided in Supplemental Table 3.

Table 3
Demographic characteristics of participants using dual-combination maintenance inhalers for asthma or COPD.

Characteristic	Asthma			COPD		
	Lower-dose ICS/LABA	Higher-dose ICS/LABA	P-value	ICS/LABA	LAMA/LABA	P-value
	N = 497	N = 285		N = 574	N = 217	
Sex, n (%)			0.167			0.594
Male	181 (36.4)	118 (41.4)		234 (40.8)	93 (42.9)	
Female	316 (63.6)	167 (58.6)		340 (59.2)	124 (57.1)	
Age (years), mean (standard deviation)	47.7 (14.9)	49.7 (15.6)	0.081	57.7 (9.5)	62.5 (10.0)	<0.001
Racial background, n (%)			0.001			0.865
White	397 (79.9)	205 (71.9)		486 (84.7)	186 (85.7)	
Black	41 (8.2)	52 (18.2)		53 (9.2)	19 (8.8)	
Asian	15 (3.0)	6 (2.1)		9 (1.6)	5 (2.3)	
Hispanic	17 (3.4)	7 (2.5)		13 (2.3)	3 (1.4)	
Other	27 (5.4)	15 (5.3)		13 (2.3)	4 (1.8)	
Employment status, n (%)			0.399			<0.001
Employed, full-time	231 (46.5)	135 (47.4)		194 (33.8)	45 (20.7)	
Employed, part-time	58 (11.7)	19 (6.7)		38 (6.6)	12 (5.5)	
Homemaker	48 (9.7)	25 (8.8)		37 (6.4)	9 (4.1)	
Student	8 (1.6)	4 (1.4)		0 (0.0)	0 (0.0)	
Unemployed	17 (3.4)	11 (3.9)		16 (2.8)	7 (3.2)	
Retired	97 (19.5)	70 (24.6)		167 (29.1)	101 (46.5)	
Disabled	37 (7.4)	20 (7.0)		118 (20.6)	38 (17.5)	
Other	1 (0.2)	1 (0.4)		4 (0.7)	5 (2.3)	
Education, n (%)			0.494			0.290
Elementary/primary school	6 (1.2)	6 (2.1)		3 (0.5)	2 (0.9)	
Secondary/high school	91 (18.3)	44 (15.4)		138 (24.0)	65 (30.0)	
Some college	142 (28.6)	95 (33.3)		195 (34.0)	58 (26.7)	
College degree	168 (33.8)	86 (30.2)		160 (27.9)	62 (28.6)	
Postgraduate degree	87 (17.5)	51 (17.9)		71 (12.4)	29 (13.4)	
Other	3 (0.6)	3 (1.1)		7 (1.2)	1 (0.5)	

P-values were calculated by analysis of variance for continuous variables and Chi-square test for categorical variables. Abbreviations: COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist.

were older (62.5 vs. 57.7 years) and less often employed full time (20.7% vs 33.8%) than patients using an ICS/LABA inhaler.

Patients with asthma using a higher-dose ICS/LABA inhaler had poorer symptom control than patients using a lower-dose ICS/LABA inhaler, as indicated by a higher median ACQ score (1.7 vs. 1.2) and a higher proportion with an ACQ score ≥1.5 (55.1% vs. 43.5%) (Table 4). Patients using a higher-dose ICS/LABA inhaler also more frequently used rescue medication (64.6% vs. 52.3% at least once weekly).

For patients with COPD, symptom impact was greater for patients using an ICS/LABA inhaler than for those using a LAMA/LABA inhaler (median CAT score = 27.0 vs. 24.0), and patients using an ICS/LABA inhaler more frequently had a high or very high symptom impact (CAT >20) than patients using a LAMA/LABA inhaler (76.0% vs. 62.7%). Patients using an ICS/LABA inhaler more often were current smokers (61.5% vs. 43.8%) and used rescue medication more frequently (70.6% vs. 65.0% at least once weekly) than patients using a LAMA/LABA inhaler.

3.2. Inhaler use

For patients with asthma on lower-dose ICS/LABA, the most common inhaler used was fluticasone propionate/salmeterol (Advair®) 250/50 μg dry powder inhaler (DPI) or 115/21 μg pressurized metered-dose inhaler (pMDI) (59.6%), followed by budesonide/formoterol 80/4.5 μg (Symbicort®) pMDI (26.2%), fluticasone furoate/vilanterol 100/25 μg (Breo®) DPI (13.3%), and mometasone/formoterol 100/5 μg (Dulera®) pMDI (4.8%) (Table 4). For patients with asthma on higher-dose ICS/LABA, the most common inhaler used was budesonide/formoterol 160/4.5 μg pMDI (38.2%), followed by fluticasone propionate/salmeterol 500/50 μg DPI or 230/21 μg pMDI (37.5%), fluticasone furoate/vilanterol 200/25 μg DPI (22.1%), and mometasone/formoterol 200/5 μg pMDI (6.3%).

For patients with COPD on LAMA/LABA, the most common inhaler used was umeclidium/vilanterol 62.5/25 μg (Anoro®) DPI (57.1%), followed by tiotropium/olodaterol 2.5/2.5 μg (Stiolto®) soft mist inhaler (26.3%), glycopyrrolate/formoterol (Bevespi®) 18/9.6 μg pMDI (15.2%), and glycopyrrolate/indacaterol 27.5/15.6 μg (Utibron®) DPI (7.8%). For patients with COPD on ICS/LABA, the most common inhaler used was fluticasone propionate/salmeterol 250/50 μg DPI (50.7%), followed by budesonide/formoterol 160/4.5 μg pMDI (43.7%) and fluticasone furoate/vilanterol 100/25 μg DPI (14.3%).

3.3. Preferences

For all treatment classes, reduced exacerbations and faster onset of action were the most important attributes to patients (Table 5). Patients with COPD on LAMA/LABA did not prefer a specific device type but preferred a dose counter every dose or a metered-dose counter over a dose counter every tenth dose.

3.4. Benefit-risk assessment

Patients with asthma on lower-dose ICS/LABA most valued the attribute combination of budesonide/formoterol pMDI followed by mometasone/formoterol pMDI, and least valued fluticasone propionate/salmeterol DPI (Fig. 1A). The preference for budesonide/formoterol pMDI in this patient group was driven mainly by its onset of action (15 min) and lower 5-year risk of osteoporosis (4.7%). The more preferred device type of pMDIs contributed to the higher predicted choice probabilities for pMDIs than for DPIs. Although priming also contributed, there was little difference in the valuation of the different priming modes of the ICS/LABA inhalers.

To switch away from budesonide/formoterol pMDI, patients in the lower-dose ICS/LABA group would need to be compensated with 3.09 fewer exacerbations per year to switch to fluticasone propionate/salmeterol DPI and 0.60 fewer exacerbations per year to switch to fluticasone furoate/vilanterol DPI. An estimated 28.4 ± 0.7% of patients in this group were expected to prefer budesonide/formoterol pMDI, 25.4 ± 0.5% to prefer mometasone/formoterol pMDI, 23.2 ± 0.7% to prefer fluticasone furoate/vilanterol DPI, 13.1 ± 0.9% to prefer fluticasone

Table 4
Clinical characteristics of participants using dual-combination maintenance inhalers for asthma or COPD.

Characteristic	Asthma			COPD		
	Lower-dose ICS/LABA	Higher-dose ICS/LABA	P-value	ICS/LABA	LAMA/LABA	P-value
	N = 497	N = 285		N = 574	N = 217	
ACQ, median (IQR)	1.2 (1–2)	1.7 (1–3)	<0.001			–
ACQ categories, n (%)			0.007			–
≤0.75	150 (30.2)	68 (23.9)		–	–	
0.75–1.5	131 (26.4)	60 (21.1)		–	–	
≥1.5	216 (43.5)	157 (55.1)		–	–	
CAT, median (IQR)	–	–	–	27 (21–32)	24 (17–31)	0.001
CAT category, n (%)			–			0.002
0–9	–	–		7 (1.2)	3 (1.4)	
10–20	–	–		131 (22.8)	78 (35.9)	
21–30	–	–		244 (42.5)	73 (33.6)	
>30	–	–		192 (33.4)	63 (29.0)	
Inhaler type, n (%)						
ICS/LABA			–			–
Budesonide/formoterol pMDI	130 (26.2)	109 (38.2)		251 (43.7)	0 (0)	
Fluticasone propionate/salmeterol DPI or pMDI	296 (59.6)	107 (37.5)		291 (50.7)	0 (0)	
Mometasone/formoterol pMDI	24 (4.8)	18 (6.3)		–	0 (0)	
Fluticasone furoate/vilanterol DPI	66 (13.3)	63 (22.1)		82 (14.3)	0 (0)	
LAMA/LABA			–			–
Glycopyrrolate/formoterol pMDI	–	–		0 (0)	33 (15.2)	
Umeclidium/vilanterol DPI	–	–		0 (0)	124 (57.1)	
Tiotropium/olodaterol soft mist inhaler	–	–		0 (0)	57 (26.3)	
Glycopyrrolate/indacaterol DPI	–	–		0 (0)	17 (7.8)	
Smoking habits, n (%)			0.762			<0.001
Current smoker	85 (17.1)	50 (17.5)		359 (62.5)	95 (43.8)	
Previous smoker	153 (30.8)	94 (33.0)		215 (37.5)	122 (56.2)	
Never smoked	259 (52.1)	141 (49.5)		0 (0)	0 (0)	
Frequency of rescue medication use, n (%)			0.006			0.044
<1/week	237 (47.7)	101 (35.4)		169 (29.4)	76 (35.0)	
1–2/week	110 (22.1)	75 (26.3)		116 (20.2)	42 (19.4)	
3–5/week	83 (16.7)	60 (21.1)		136 (23.7)	36 (16.6)	
6–10/week	33 (6.6)	30 (10.5)		79 (13.8)	29 (13.4)	
>10/week	25 (5.0)	18 (6.3)		53 (9.2)	17 (7.8)	
Don't know	9 (1.8)	1 (0.4)		21 (3.7)	17 (7.8)	
Overall health, n (%)			0.086			0.916
Very poor	4 (0.8)	9 (3.2)		28 (4.9)	8 (3.7)	
Poor	29 (5.8)	20 (7.0)		117 (20.4)	44 (20.3)	
Fair	178 (35.8)	94 (33.0)		299 (52.1)	115 (53.0)	
Good	222 (44.7)	118 (41.4)		123 (21.4)	46 (21.2)	
Very good	64 (12.9)	44 (15.4)		7 (1.2)	4 (1.8)	

P-values were calculated by analysis of variance for continuous variables and Chi-square test for categorical variables. Abbreviations: ACQ, Asthma Control Questionnaire; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; ICS, inhaled corticosteroid; IQR, interquartile range; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; pMDI, pressurized metered-dose inhaler.

propionate/salmeterol pMDI, and 10.0 ± 1.0% to prefer fluticasone/salmeterol DPI (Fig. 1B).

Patients with asthma on higher-dose ICS/LABA placed similar values on the different treatments as those in the lower-dose ICS/LABA group, although mometasone/formoterol pMDI had a marginally higher overall value than budesonide/formoterol pMDI (Fig. 2A). Budesonide/formoterol pMDI performed better than mometasone/formoterol pMDI for 5-year risk of osteoporosis. Attribute profiles of mometasone/formoterol pMDI and budesonide/formoterol pMDI are similar, although mometasone/formoterol pMDI has a dose counter that counts every dose and budesonide/formoterol pMDI has a dose counter that counts every tenth dose. Because patients in this group preferred a dose counter that counts every dose over one that counts every tenth dose, the value for mometasone/formoterol pMDI was higher in this group than in the lower-dose ICS/LABA group, in which patients did not have significant preferences for either of the two dose counters. To switch away from mometasone/formoterol pMDI or budesonide/formoterol pMDI, patients in this group would require 2.77 fewer exacerbations per year to switch to fluticasone propionate/salmeterol DPI and 0.85 fewer exacerbations per year to switch to fluticasone furoate/vilanterol DPI. An estimated 27.0 ± 0.7% of patients in this group were expected to prefer the combination of attributes of mometasone/formoterol pMDI, 26.9 ± 1.0% to prefer those in budesonide/formoterol pMDI, 20.1 ± 1.0% to prefer those in fluticasone/vilanterol DPI, 15.6 ± 1.1% to prefer those in fluticasone/salmeterol pMDI, and 10.4 ± 1.3% to prefer those in fluticasone/salmeterol DPI (Fig. 2B). Fluticasone propionate/salmeterol DPI was the least preferred inhaler for patients with asthma on higher-dose ICS/LABA due to the slow onset time (30 min), twice-daily dosing, and being a dry powder inhaler.

For patients with COPD on ICS/LABA, budesonide/formoterol pMDI was the most valued inhaler (Fig. 3A). This was mainly driven not only by its fast onset of action but also by a lower risk of osteoporosis and pneumonia. To switch from budesonide/formoterol pMDI, patients in this group were estimated to require 2.20 fewer exacerbations per year to switch to fluticasone propionate/salmeterol DPI and 1.70 fewer exacerbations per year to switch to fluticasone furoate/vilanterol DPI. To switch from fluticasone furoate/vilanterol DPI to fluticasone propionate/salmeterol DPI, patients in this group were estimated to require 0.50 fewer exacerbations per year. An estimated 56.6 ± 1.8% of patients in this group were expected to prefer budesonide/formoterol pMDI, mainly driven by a faster onset of action and lower 5-year risk of pneumonia than the comparators (Fig. 3B). An estimated 24.4 ± 1.2% were expected to prefer fluticasone/vilanterol DPI and 19.0 ± 1.0% to prefer fluticasone/salmeterol DPI.

For patients with COPD on LAMA/LABA, tiotropium/olodaterol soft mist inhaler was the most valued and had the highest preferred choice

Table 5
Multinomial logit model for each cohort.

Attribute	Coefficient estimate (standard error)			
	Asthma		COPD	
	Lower-dose ICS/LABA	Higher-dose ICS/LABA	ICS/LABA	LAMA/LABA
Constant (left alternative)	0.102*** (0.028)	0.242*** (0.037)	0.049 (0.026)	−0.003 (0.045)
Exacerbations (per decrease of 1 exacerbation)	0.339*** (0.021)	0.343*** (0.027)	0.497*** (0.020)	0.709*** (0.036)
Onset time (per 1-min decrease)	0.044*** (0.002)	0.036*** (0.003)	0.041*** (0.002)	0.044*** (0.003)
5-year risk of osteoporosis (per % decrease)	0.247*** (0.022)	0.188*** (0.028)	0.164*** (0.020)	0.139*** (0.034)
Dosing frequency				
Twice daily	Reference	Reference	Reference	Reference
Once daily	0.183*** (0.033)	0.112* (0.044)	0.127*** (0.032)	0.365*** (0.057)
Priming				
Capsule	Reference	Reference	Reference	Reference
Canister: 2 steps	0.431*** (0.047)	0.340*** (0.061)	0.340*** (0.042)	0.526*** (0.074)
Discharge: 1 step	0.378*** (0.052)	0.366*** (0.068)	0.297*** (0.053)	0.298** (0.094)
1 or 2 easy steps	0.444*** (0.051)	0.349*** (0.066)	0.367*** (0.052)	0.492*** (0.091)
Inhaler device type				
Dry powder inhaler	Reference	Reference	Reference	0.004 (0.064)
Soft mist inhaler	0.213*** (0.039)	0.292*** (0.052)	0.093* (0.037)	Reference
Pressurized inhaler	0.340*** (0.040)	0.351*** (0.053)	0.254*** (0.038)	0.045 (0.064)
Dose counter				
Metered	Reference	Reference	Reference	0.219*** (0.064)
Every 10th dose	0.037 (0.040)	0.020 (0.052)	0.037 (0.040)	Reference
Every dose	0.057 (0.042)	0.122* (0.054)	0.057 (0.042)	0.355*** (0.068)
5-year risk of pneumonia (per % decrease)	N/A	N/A	0.058*** (0.004)	0.071*** (0.007)
Number of patients	497	285	574	217
McFadden's R^2	0.109	0.100	0.109	0.185

For attributes with reference levels, the coefficient estimates indicate the utility that would be gained by a patient if they switched from the reference level to another level. Abbreviations: COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; N/A, not applicable. *P < 0.05, **P < 0.01, ***P < 0.001.

probability (42.3 ± 2.2%) due to its rapid onset of action, once-daily dosing, preferred priming method, and dose counter that counts every dose (Fig. 4A). Preferred choice probabilities were similar for glycopyrrolate/indacaterol DPI (20.0 ± 1.3%), glycopyrrolate/formoterol pMDI (19.7 ± 1.3%), and umeclidinium/vilanterol DPI (18.0 ± 3.6%) (Fig. 4B). Glycopyrrolate/formoterol pMDI had a lower choice probability than tiotropium/olodaterol soft mist inhaler due to twice-daily dosing and having a dose counter that counts every tenth dose. For a patient to switch away from tiotropium/olodaterol soft mist inhaler, they would need to be compensated with 1.08 fewer exacerbations per year to switch to glycopyrrolate/formoterol pMDI, 1.06 fewer exacerbations per year to switch to glycopyrrolate/indacaterol DPI, and 1.20 fewer exacerbations per year to switch to umeclidium/vilanterol DPI.

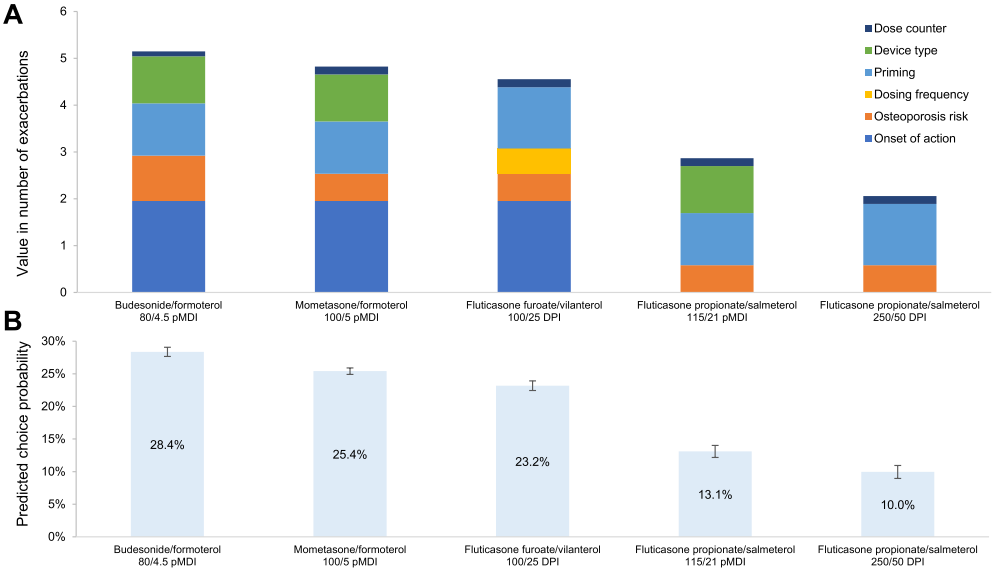

Fig. 1. Value in number of exacerbations (A) and predicted choice probabilities (B) for lower-dose ICS/LABA maintenance inhalers in patients with asthma.
Value in number of exacerbations represents how many additional exacerbations a patient would be willing to accept each year to switch from an inhaler with the reference level attributes to an inhaler with the indicated attribute levels. Abbreviations: DPI, dry powder inhaler; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; pMDI, pressurized metered-dose inhaler.

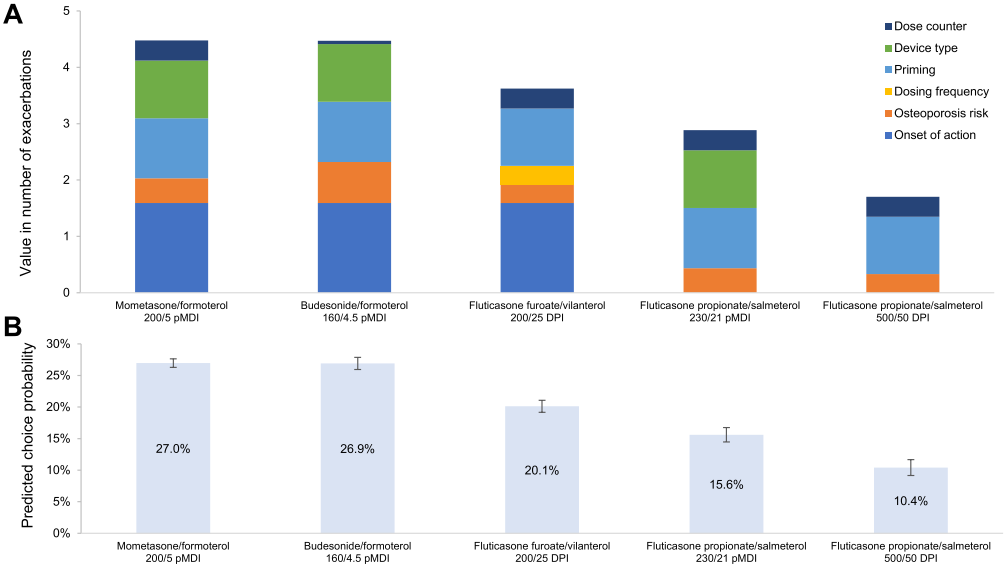

Fig. 2. Value in number of exacerbations (A) and predicted choice probabilities (B) for higher-dose ICS/LABA maintenance inhalers in patients with asthma. Value in number of exacerbations represents how many additional exacerbations a patient would be willing to accept each year to switch from an inhaler with the reference level attributes to an inhaler with the indicated attribute levels. Abbreviations: DPI, dry powder inhaler; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; pMDI, pressurized metered-dose inhaler.

4. Discussion

Our previous analysis of the full-sample DCE showed that, for patients with asthma or COPD, the most important attributes of dual-combination maintenance inhalers were a faster onset of action and reduced exacerbations [4]. The current study, which separated participants according to disease and maintenance inhaler class used, found that participant subclasses differed only in their preferences for device type and dose counter, which were among the least valued attributes. Importantly, the predicted choice probabilities for each patient class mostly did not match the proportions of patients prescribed each inhaler. For example, for patients with asthma, mometasone/formoterol was predicted to be one of the most preferred inhalers but was the least prescribed. For patients with COPD on ICS/LABA, fluticasone propionate DPI was the most prescribed but the least preferred. Similarly, for patients with COPD on LAMA/LABA, umeclidium/vilanterol DPI was the most prescribed but least preferred. This suggests that current practice may not allow patients to identify their preferred inhaler. These differences between inhaler prescriptions may be influenced by the extent to which they are reimbursed by insurance [6].

Differences between the predicted preferences and actual prescriptions highlight the importance of considering the patient

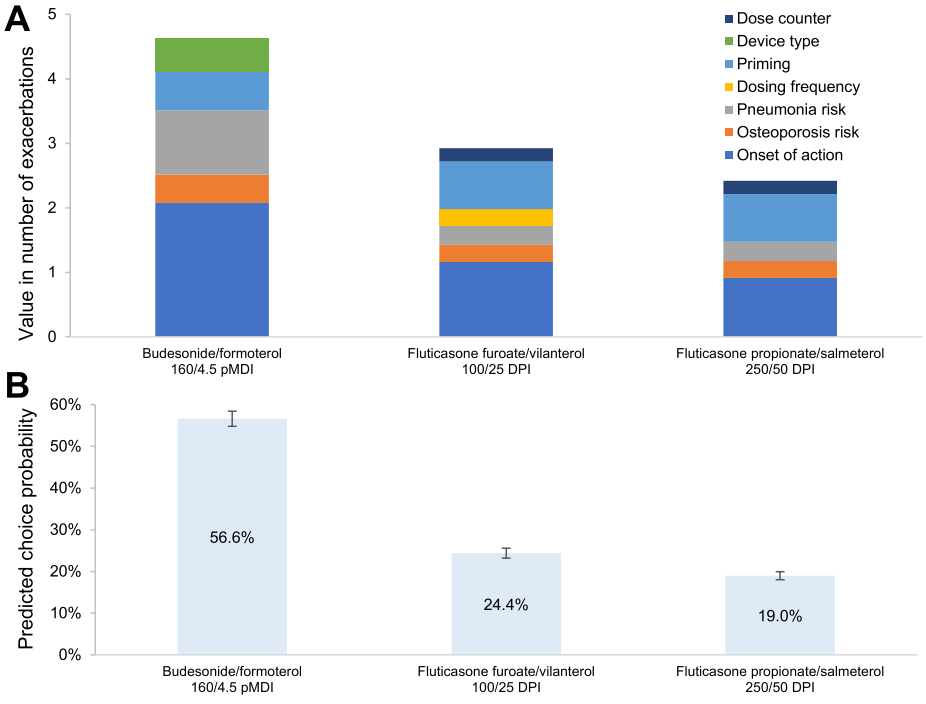

Fig. 3. Value in number of exacerbations (A) and predicted choice probabilities (B) for ICS/LABA maintenance inhalers in patients with chronic obstructive pulmonary disease. Value in number of exacerbations represents how many additional exacerbations a patient would be willing to accept each year to switch from an inhaler with the reference level attributes to an inhaler with the indicated attribute levels. Abbreviations: DPI, dry powder inhaler; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; pMDI, pressurized metered-dose inhaler.

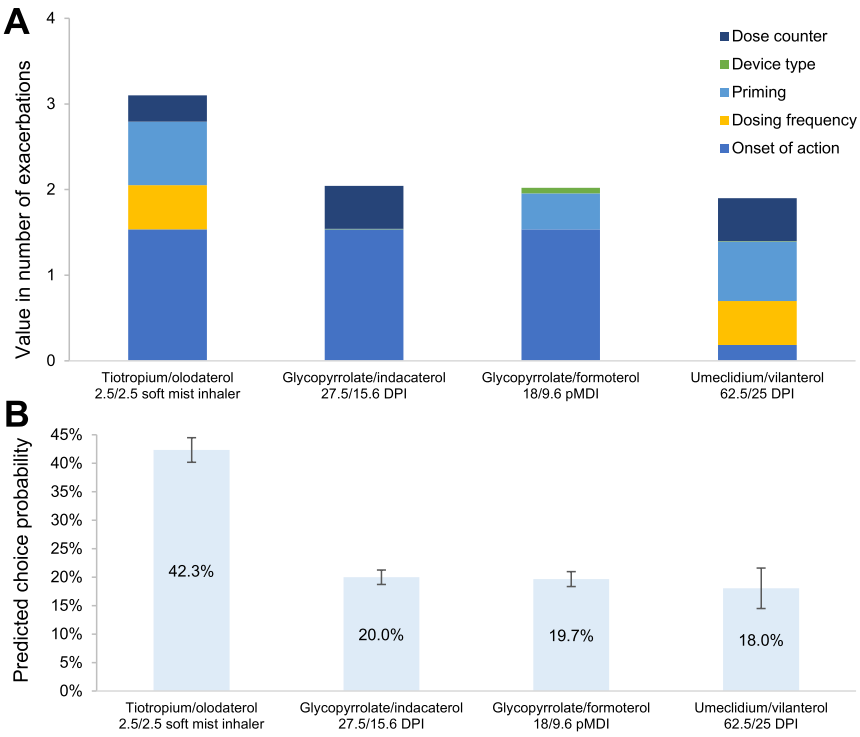

Fig. 4. Value in number of exacerbations (A) and predicted choice probabilities (B) for LAMA/LABA maintenance inhalers in patients with chronic obstructive pulmonary disease.
Value in number of exacerbations represents how many additional exacerbations a patient would be willing to accept each year to switch from an inhaler with the reference level attributes to an inhaler with the indicated attribute levels. Abbreviations: DPI, dry powder inhaler; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; pMDI, pressurized metered-dose inhaler.

perspective when selecting a maintenance inhaler for each patient. Shared decision-making between health care providers and patients empowers patients in their own care and can lead to improved adherence and outcomes, especially when the best choice is not clear [7,8]. Although shared decision making in the clinic can lead to greater patient satisfaction, the time allocated to clinical consultation does not usually allow for preferences to be formally elicited. In such cases, benefit-risk data can help guide shared decision-making [9].

There are some limitations to the current analysis and, in general, to using any preference-based benefit-risk assessment to guide shared decision-making. Direct comparison of the different treatment options may provide more credible ranking than the indirect benefit-risk approach taken in this paper. Patient preferences captured with stated preference methods can have limited external validity, although recent research has shown that DCEs can predict actual choices in health [10]. Preferences may differ for patients with a worse disease status, a different culture, or different lifestyles. This study found some differences between patient subgroups, for example, in racial background and disease severity in patients with asthma using lower-dose versus higher-dose ICS/LABA inhalers, and in employment status of patients with COPD using ICS/LABA versus LAMA/LABA inhalers. However, the overall preferences were similar for all four groups of patients. Another potential limitation of any benefit-risk assessment is that predicted choice probabilities depend on accurate measurement of both patient preferences and treatment performance. To reduce the chance of inaccuracies, the internal validity of the DCE questionnaire was confirmed based on answers to dominated-choice and repeated questions. Also, attributes and levels were selected based on a previous patient focus group study [5], coupled with a literature search and expert clinical advice, to ensure that the DCE would capture the patient perspective. Although treatment performance estimates are, by definition, accurate for categorical convenience attributes such as dosing frequency, they are less accurate for clinical attributes, because safety and efficacy of different inhalers have not been compared head-to-head in clinical trials. Finally, our results are dependent on the attributes included in the DCE. Although the attributes and their levels were selected considering the patient perspective, the findings need to be interpreted in the context of these attributes. Selection of different benefit, risks or convenience attributes may result in changes in the treatment ranking.

In summary, this study illustrates how patient preferences for dual-combination maintenance inhaler attributes can be used to identify which maintenance inhalers within each treatment class patients prefer. The study also revealed important differences between patient preferences and what the patient was taking, which highlights the importance of considering the patient's perspective and shared decision-making when prescribing a maintenance inhaler.

CRediT authorship contribution statement

Tommi Tervonen: Conceptualization, Methodology, Investigation, Validation, Writing - original draft, Supervision. **Fernando J. Martinez:** Investigation, Writing - review & editing. **Nicola A. Hanania:** Investigation, Writing - review & editing. **Sebastian Heidenreich:** Methodology, Software, Formal analysis, Writing - review & editing. **James M. Eudicone:** Validation, Writing - review & editing. **Ileen Gilbert:** Conceptualization, Methodology, Investigation, Writing - original draft, Funding acquisition.

Declaration of competing interest

IG and JME are employees of AstraZeneca, the study sponsor. TT and SH are employees of Evidera, which was paid by AstraZeneca for work related to this study. NAH has received research funds (to his institution) from AstraZeneca, GlaxoSmithKline (GSK), Boehringer Ingelheim, Gossamer Bio, Genentech, Novartis, and Sanofi Genzyme. He has received honoraria for serving on advisory boards for AstraZeneca, GSK, Boehringer Ingelheim, Sanofi Genzyme, Mylan, Novartis, Theravance, Sunovion, and Genentech. FJM reports personal fees from Adept, Afferent, Amgen, AstraZeneca, Axon, Axon Communication, Boehringer Ingelheim, Clarion, ConCert, Forest, Genentech, GlaxoSmithKline, Ikaria/Bellerophon, Informa, Janssen, Kadmon, Lucid, Methodist Hospital, Novartis, Nycomed/Takeda, Pearl Therapeutics, Inc., Pfizer, Prime,

Roche, Sunovion, Theravance, Unity Biotechnology, Veracyte, and WebMD; has received royalty fees from Informa; and has spoken on behalf of AstraZeneca and Nycomed/Takeda.

Acknowledgements

Medical writing was provided by Dr. Phillip Leventhal (Evidera) and funded by AstraZeneca. The authors thank Durgesh Bhandary (AstraZeneca) for useful comments on the analyses and Haidong Feng and Caitlin Thomas (Evidera) for analytical support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2020.106278.

References

[1] Global Initiative for Chronic Obstructive Lung Disease, Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2019 Report) Fontana, WI: Global Initiative for Chronic Obstructive Lung Disease, 2019. Available from: https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf.

[2] National Institutes of Health, National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, U. S. Department of Health and Human Services, Washington, D.C., 2007.

[3] V. Soekhai, E.W. de Bekker-Grob, A.R. Ellis, C.M. Vass, Discrete choice experiments in health economics: past, present and future, Pharmacoeconomics 37 (2) (2019) 201–226.

[4] T. Tervonen, N. Hawken, N.A. Hanania, F.J. Martinez, S. Heidenreich, I. Gilbert, Maintenance inhaler therapy preferences of patients with asthma or chronic obstructive pulmonary disease: a discrete choice experiment, Thorax 75 (9) (2020) 735–743.

[5] N.A. Hanania, N. Hawken, I. Gilbert, F.J. Martinez, K.M. Fox, M.M. Ross, et al., What symptomatic patients with asthma and chronic obstructive pulmonary disease (COPD) find important in their maintenance inhaler therapy: a focus group study. Poster C37, Am. J. Respir. Crit. Care Med. 197 (2018) A4863.

[6] G.F. Joyce, J.J. Escarce, M.D. Solomon, D.P. Goldman, Employer drug benefit plans and spending on prescription drugs, J. Am. Med. Assoc. 288 (14) (2002) 1733–1739.

[7] M.S. Blaiss, G.C. Steven, B. Bender, D.A. Bukstein, E.O. Meltzer, T. Winders, Shared decision making for the allergist, Ann. Allergy Asthma Immunol. 122 (5) (2019) 463–470.

[8] S. Pollard, N. Bansback, J.M. FitzGerld, S. Bryan, The burden of nonadherence among adults with asthma: a role for shared decision-making, Allergy 72 (5) (2017) 705–712.

[9] T. Tervonen, A. Angelis, K. Hockley, F. Pignatti, L.D. Phillips, Quantifying preferences in drug benefit-risk decisions, Clin. Pharmacol. Ther. 106 (5) (2019) 955–959.

[10] E.W. de Bekker-Grob, J.D. Swait, H.T. Kassahun, M.C.J. Bliemer, M.F. Jonker, J. Veldwijk, et al., Are healthcare choices predictable? The impact of discrete choice experiment designs and models, Value Health 22 (9) (2019) 1050–1062.