Single-Inhaler Triple Therapies for Asthma and Chronic Obstructive Pulmonary Disease

Individual Topic Request

DERP Governance Call

December 1, 2022

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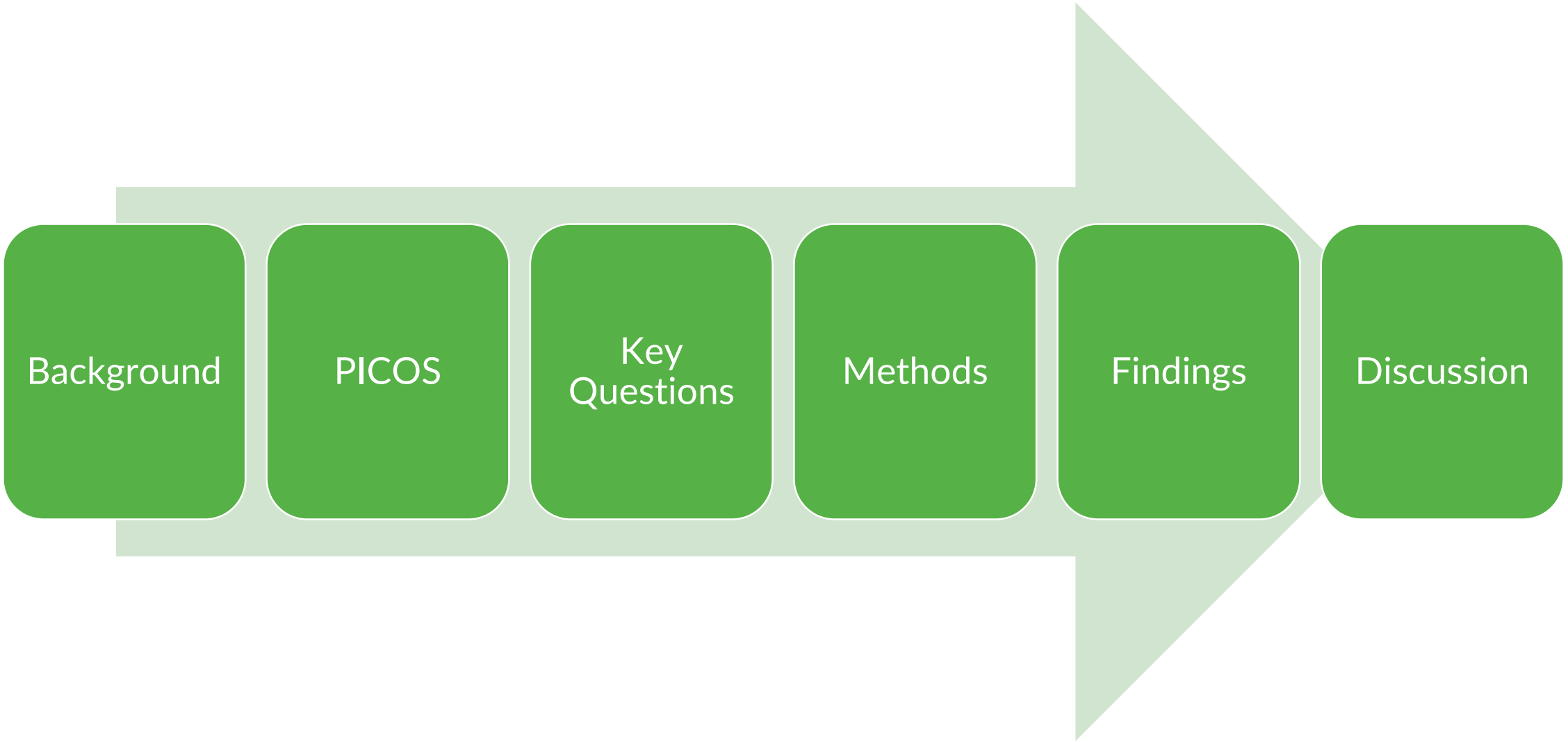
OHSU

Overview


Background
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Discussion

Background: Asthma

- Affects 1 in 13 (~8%) Americans
- More likely to have asthma:
  - Females (9.4% vs. 6.5% male)
  - Non-White and Non-Hispanic
  - Puerto Rican
  - Federal poverty threshold
  - Live in an urban area
- Children attending schools with poor infrastructure have:
  - Worse asthma-related health outcomes
  - Higher rates of asthma-related absenteeism
  - Higher rates of asthma-related hospitalization

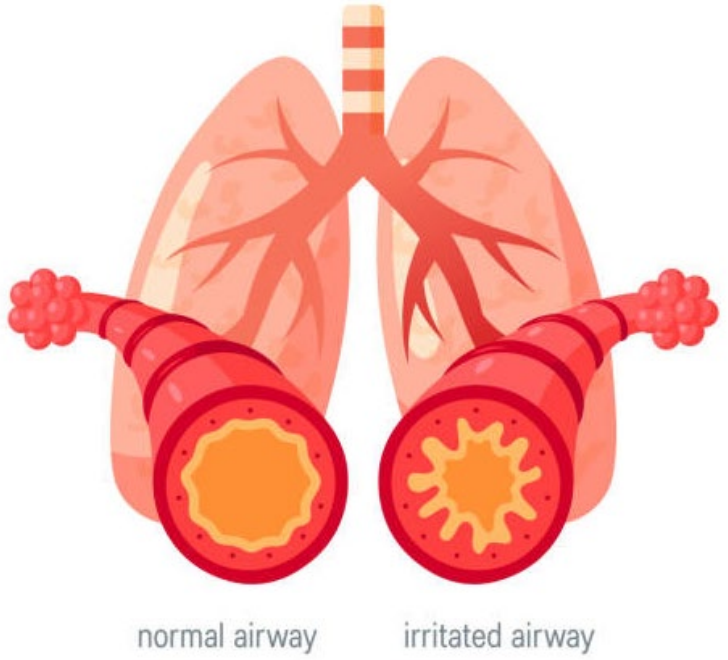

Image source: istockphoto

Background: COPD

- Affects 12.5 million US adults (~5%)
  - Highest rates in the Midwest (~12%)
- Comorbidities very common
- More likely to have COPD:
  - Women
  - Non-White and Non-Hispanic
  - Aged 65 or older
  - Current or former smoker
  - Live in an urban area
  - Low socioeconomic status
- Mortality
  - Higher in women
  - Nearly double in rural areas (74 vs. 40 urban per 100k deaths)

Image source: National Institutes of Health

Background: Medicaid

- Expansion improved coverage, but barriers remain (e.g., access to health care provider, costs)
- 2018 review of Medicaid coverage of guidelines-based care lacking and inconsistent
- Between 2012 and 2018:
  - Prescriptions filled for inhaled corticosteroids increased 77%
  - Spending on inhalers doubled ($2.1 billion to $4.6 billion)
  - Total spending in 7-year period: $26.2 billion

Image source: Livestrong

Abbreviations

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- ACQ-7: Asthma Control Questionnaire, 7-item
- AE: adverse event
- BDP: beclomesthasone
- BUD: budesonide
- CFB: change from baseline
- FEV_1: forced expiratory volume in 1 second
- FLU: fluticasone
- FOR: formoterol
- GLY: glycopyrrolate/glycopyrronium
- HRQoL: health-related quality of life
- MCID: minimal clinically important difference
- MITT: multiple-inhaler triple therapy
- SGRQ: St. George's Respiratory Questionnaire
- SITT: single-inhaler triple therapy
- TIO: tiotropium
- UMEC: umeclidinium
- VI: vilanterol

PICOS

- Populations: Adults and children with COPD or asthma
- Interventions:

Brand Name	Generic Name	Indication(s)	FDA Approval Date
Breztri Aerosphere (BUD/GLY/FOR)	Budesonide; glycopyrrolate; formoterol fumarate	• COPD • *Asthma (pipeline therapy)*	07/23/2020
Trelegy Ellipta (FLU/UMEC/VI)	Fluticasone furoate; umeclidinium bromide; vilanterol trifenatate	• COPD • Asthma (aged ≥ 18 years)	09/18/2017
Pipeline Therapies			
Trimbow (BDP/GLY/FOR)	Beclomethasone dipropionate; glycopyrronium bromide; formoterol fumarate dihydrate	• COPD • Asthma	N/A

Abbreviations. COPD: chronic obstructive pulmonary disease; FDA: US Food & Drug Administration; N/A: not applicable.

PICOS

- Comparators:
  - Another listed intervention
  - Standard of care (e.g., monotherapy, dual therapy, or MITTs)
- Outcomes:
  - Lung function (e.g., FEV_1)
  - Severe exacerbations
  - Symptom control
  - Use of rescue medication
  - Quality of life (e.g., SGRQ)
  - AEs (including serious AEs [SAEs], hospital admissions, emergency visits)
  - Mortality
- Study Designs:
  - Randomized controlled trials (RCTs)

Key Questions

For SITTs for asthma and COPD:

1. Effectiveness
2. Harms
3. Subgroup variations in effectiveness or harms
4. Ongoing studies

Methods

Methods

Clinical evidence sources searched September 15, 2022

- Ovid MEDLINE ALL
- The Cochrane Library

Reference list review

- Systematic reviews
- Included studies

Risk of bias

- RCTs assessed with standard forms

Ongoing studies

- Clinical trial registries (e.g., ClinicalTrials.gov)

DERP Risk of Bias Assessment

- **Low**

  Clear reporting of methods and mitigation of potential biases and conflicts of interest

- **Moderate**

  Incomplete information about methods that might mask important limitations or a meaningful conflict of interest

- **High**

  Clear flaws that might introduce serious bias

Findings

Overview

Minimal Clinically Important Differences

Measure	Condition(s)	Score Range	MCID (from baseline)
Lung Function			
Trough FEV_1	Asthma COPD	N/A	≥ 100 ml increase
Symptoms			
Exacerbations	Asthma COPD	N/A	None currently exist.
Health-Related Quality of Life			
ACQ-7 total score	Asthma	0 to 6 Higher score indicates more severely uncontrolled	≥ 0.5 points decrease
CAT total score	COPD	0 to 40 Higher score indicates more limitations	Not yet determined.
SGRQ total score	Asthma COPD	0 to 100 Higher score indicates more limitations	≥ 4 units decrease

Abbreviations. ACQ-7: Asthma Control Questionnaire, 7-item; CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; MCID: minimal clinically important difference; N/A: not applicable; SGRQ: St. George's Respiratory Questionnaire.

Findings: Study Characteristics

Comparators	Condition	Number of RCTs	Study Size Range	Total N	Study Duration (weeks)
Trelegy vs. FLU/VI	Asthma	1	N/A	2,436	24 to 52
Breztri vs. dual therapies	COPD	2	1,902 and 8,588	10,490	24 to 52
Trelegy vs. mono, dual, or MITTs	COPD	7	732 to 10,355	18,590	12 to 52
Trimbow vs. mono, dual, or MITTs	COPD	2	708 to 2,691	3,399	24 to 52
Total		**12** in 26 publications	**17 to 1,323**	**34,915**	**12 to 52**

Abbreviations. COPD: chronic obstructive pulmonary disease: FLU: fluticasone; MITT: multi-inhaler triple therapy; RCT: randomized controlled trial; VI: vilanterol.

Key Findings

- **In general,** compared with monotherapy or dual therapy, **Breztri, Trelegy, and Trimbow demonstrated improvements** in:
  - Lung function (i.e., trough FEV_1)
  - Frequency of moderate-to-severe exacerbations
  - Delay in time-to-first moderate or severe exacerbations
  - Frequency and volume of rescue medication use
  - HRQoL
- Non-inferior when compared with MITTs
- Rate and type of AEs, SAEs, and AEs of special interest (e.g., pneumonia) were similar among all treatments
- Early withdrawals due to AEs and deaths were rare

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Findings

Asthma

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Asthma Findings: Characteristics of Included RCT

Study Name Location(s) Study Duration Risk of Bias	N Randomized Participant Characteristics	Treatments

CAPTAIN
US + multinational
24 to 52 weeks
Moderate
	• N = 2,439
	• Mean age: 53.2 (SD, 13.1)
	• Male: 922 (38%)
	• Race
	  ○ White: 1,950 (80%)
	  ○ Asian: 344 (14%)
	  ○ Black/AA: 119 (5%)
		• Trelegy (UMEC 31.25 µg), n = 809
		• Trelegy (UMEC 62.5 µg), n = 814
		• FLU/VI, n = 813

Abbreviations. AA: African American; FLU: fluticasone; SD: standard deviation; UMEC: umeclidinium; VI: vilanterol.

Asthma Findings: Lung Function and Exacerbations Over 24 Weeks

Outcome	Trelegy (UMEC 31.25 µg)	Trelegy (UMEC 62.5 µg)	FLU/VI
Lung Function			
Trough FEV_1, mean CFB	139 ml (95% CI, 117 to 161)	151 ml (95% CI, 129 to 172)	50 ml (95% CI, 28 to 72)
Trough FEV_1, mean between-treatment difference	89 ml (95% CI, 58 to 120); *P* < .001	101 ml (95% CI, 70 to 132); *P* < .001	N/A
Exacerbations			
Experienced ≥ 1 moderate or severe exacerbations during study	367 (45.4%); 185 severe events	329 (40.4%); 182 severe events	379 (46.6%); 179 severe events
Annualized rate of severe exacerbations, over 52 weeks	adjusted rate ratio, 0.99 (95% CI, 0.77 to 1.29); *P* = 1.0	adjusted rate ratio, 0.97 (95% CI, 0.75 to 1.26); *P* = .8	N/A

Note. Shaded boxes indicate statistically significant findings.
Abbreviations. CFB: change from baseline; CI: confidence interval; FEV_1: forced expiratory volume in 1 second; FLU: fluticasone; N/A: not applicable; UMEC: umeclidinium; VI: vilanterol.

Asthma Findings: Rescue Medication Use Over 24 Weeks

Outcome	Trelegy (UMEC 31.25 µg)	Trelegy (UMEC 62.5 µg)	FLU/VI
Percentage of rescue-free days, mean CFB	13.72 (95% CI, 12.08 to 15.35)	13.11 (95% CI, 11.48 to 14.74)	10.94 (95% CI, 9.29 to 12.59)
Percentage of rescue-free days, mean between-treatment difference	2.78 (95% CI, 0.45 to 5.10); *P* = .02	2.17 (95% CI, −0.15 to 4.49); *P* = .07	N/A
Puffs per day, mean	1.5 (SD, 2.04); mean CFB, −0.5 (95% CI, −0.6 to −0.5)	1.4 (SD, 1.92); mean CFB, −0.4 (95% CI, −0.5 to −0.4)	1.4 (SD, 1.95); mean CFB, −0.4 (95% CI, −0.4 to −0.3)
Puffs per day, mean between-treatment difference	−0.2 (95% CI, −0.2 to −0.1); *P* < .001	0 (95% CI, −0.1 to 0.0); *P* = .3	N/A

Note. Shaded boxes indicate statistically significant findings.
Abbreviations. CFB: change from baseline; CI: confidence interval; FLU: fluticasone; N/A: not applicable; UMEC: umeclidinium; VI: vilanterol.

Asthma Findings: Health-Related Quality of Life at 24 Weeks

Outcome	Trelegy (UMEC 31.25 µg)	Trelegy (UMEC 62.5 µg)	FLU/VI
ACQ-7, total score mean CFB	−0.73 (95% CI, −0.78 to −0.69)	−0.77 (95% CI, −0.81 to −0.72)	−0.68 (95% CI, −0.73 to −0.63)
ACQ-7, total score mean between-treatment difference	−0.06 (95% CI, −0.12 to 0.01); *P* = .1	−0.09 (95% CI, −0.16 to −0.02); *P* = .008	N/A
ACQ-7, responder rate	OR, 1.15 (95% CI, 0.94 to 1.42); *P* = .2	OR, 1.43 (95% CI, 1.16 to 1.76); *P* < .001	N/A
SGRQ total score mean CFB	−10.29 (95% CI, −11.26 to −9.32)	−11.69 (95% CI, −12.64 to −10.73)	−11.39 (95% CI, −12.35 to −10.42)
SGRQ total score mean between-treatment difference	1.10 (95% CI, −0.27 to 2.47); *P* = .1	−0.30 (95% CI, −1.66 to 1.05); *P* = .7	N/A
Responder rate	OR, 0.86 (95% CI, 0.69 to 1.06); *P* = .1	OR, 1.14 (95% CI, 0.92 to 1.42); *P* = .2	N/A

Note. Shaded boxes indicate statistically significant findings.
Abbreviations. ACQ-7: Asthma Control Questionnaire, 7-item; CFB: change from baseline; CI: confidence interval; FLU: fluticasone; N/A: not applicable; OR: odds ratio; SGRQ: St George's Respiratory Questionnaire; UMEC: umeclidinium; VI: vilanterol.

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Findings

COPD

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Overview of Included RCTs For COPD

Study	Duration	Includes US	N Randomized	Comparators	Mean Age	Lung Function (e.g., FEV_1)	Symptom Control	HRQoL (e.g., SGRQ)	Adverse Events	Risk of Bias
Breztri										
ETHOS	52	√	8,588	• BUD/FOR • GLY/FOR	64.6	√	√	√	√	High
KRONOS	24	√	1,902	• BUD/FOR • GLY/FOR	65.2	√	√	√	√	Moderate
Trelegy										
Bansal, 2021	12	√	800	• TIO	66.1	√	√	√	√	Moderate
Bremner, 2018	24	X	1,055	• FLU/VI+UMEC	66.3	√	√	√	√	High
[a]Ferguson, 2020	12	√	729	• BUD/FOR+TIO	65.1	√	√	√	√	Moderate
[a]Ferguson, 2020	12	√	732	• BUD/FOR+TIO	65.3	√	√	√	√	Moderate
FULFIL	24	X	1,810	• BUD/FOR	63.9	√	√	√	√	Moderate
IMPACT	52	√	10,355	• FLU/VI • UMEC/VI	65.3	√	√	√	√	High
INTREPID	24	X	3,109	• Any MITT	67.8	√	√	√	√	High
Trimbow										
TRINITY	52	X	2,691	• TIO • BDP/FOR+TIO	63.2	√	√	√	√	Moderate
TRIVERSYTI	24	X	708	• BUD/FOR	65.9	√	√	√	√	Moderate

Note. [a] Ferguson and colleagues report 2 replicate RCTs in the same publication. Abbreviations. BDP: beclomethasone dipropionate; BUD: budesonide; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; FLU: fluticasone; FOR: formoterol; GLY: glycopyrronium; HRQoL: health-related quality of life; MITT: multiple-inhaler triple therapy; RCT: randomized controlled trial; SGRQ: St. George's Respiratory Questionnaire; SITT: single-inhaler triple therapy; TIO: tiotropium; UMEC: umeclidinium; VI: vilanterol.

COPD Findings: Characteristics of Included Breztri RCTs

Study Name Study Duration Risk of Bias	N Randomized Participant Characteristics	Treatments

ETHOS
52 weeks
High
	• N = 8,588[a]
	• Moderate-to-very-severe COPD
	• Mean age: 64.6 years (SD, 7.6)
	• Male: 5,081 (63%)
	• Current smoker: 3,495 (40.7%)
	• White: 7,226 (84.9%)
		• Breztri (BUD/GLY/FOR)
		  ○ 320/9/4.8 µg, n = 2,157
		  ○ 160/9/4.8 µg, n = 2,137
		• GLY/FOR (9/4.8 µg), n = 2,143
		• BUD/FOR (160/4.8 µg), n = 2,151

KRONOS 24 weeks Moderate	• N = 1,902 • Moderate-to-very-severe COPD • Mean age: 65.2 (SD, 7.6) • Male: 1,350 (71.2%) • Current smoker: 750 (39.5%) • White: 950 (50.1%) • Asian: 852 (44.9%)	• Breztri (BUD/GLY/FOR) ○ 320/14.4/10 µg, n = 639 • GLY/FOR (18/9.6 µg), n = 625 • BUD/FOR_{MDI}[b] (320/9.6 µg), n = 314 • BUD/FOR_{DPI}[b] (400/12 µg), n = 318

Note. [a] ETHOS reports participant characteristics and analyses with a modified intention to treat population (N = 8,509). [b] KRONOS used an MDI and DPI formulation of BUD/FOR due to differences in availability of the MDI version among participating countries.
Abbreviations. BUD: budesonide; COPD: chronic obstructive pulmonary disease; DPI: dry-powder inhaler; FOR: formoterol; GLY: glycopyrrolate; MDI: metered-dose inhaler; RCT: randomized controlled trial; SD: standard deviation.

COPD Findings: Breztri, Lung Function Over 24 Weeks

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		Breztri versus	
Outcome	Breztri	GLY/FOR	BUD/FOR
Trough FEV_1, mean CFB	147 ml	125 ml	73 to 88 ml
Trough FEV_1, mean between-group difference	N/A	22 ml; *P* = .01	59 to 74 ml; *P* < .001
Time to clinically important deterioration[a]	N/A	HR, 0.88; *P* = .06	HR, 0.81 to 0.83; *P* ≤ .03
Subgroup of very severe COPD participants (n = 3,088)			
FEV_1, mean between-group difference	NR	30 to 43 ml; *P* < .001	63 to 76 ml; *P* < .001

Note. Shaded boxes indicate statistically significant findings. [a] *Clinically important deterioration defined as a decrease of ≥ 100 ml from baseline trough* FEV_1.
Abbreviations. BUD: budesonide; CFB: change from baseline; FEV_1*: forced expiratory volume in 1 second; FOR: formoterol; GLY: glycopyrrolate; HR: hazard ratio; N/A: not applicable.*

COPD Findings: Breztri, Moderate-to-Severe Exacerbations

		Breztri versus	
Outcome	Breztri	GLY/FOR	BUD/FOR
Over 24 weeks			
Annual Rate	0.46	0.95	0.55 to 0.56
Annual Rate Ratio	N/A	0.48; *P* < .001	0.82; *P* = .3
Time-to-First	N/A	HR, 0.59; *P* < .001	HR, 0.75; *P* = .06
Over 52 weeks			
Annual Rate	1.08	1.42	1.24
Annual Rate Ratio	N/A	0.76; *P* < .001	0.86; *P* ≤ .003
Time-to-First	N/A	HR, 0.88; *P* ≤ .004	HR, 0.89; *P* ≤ .01

Note. Shaded boxes indicate statistically significant findings.
Abbreviations. BUD: budesonide; FOR: formoterol; GLY: glycopyrrolate; HR: hazard ratio; N/A: not applicable.

COPD Findings: Breztri, Rescue Medication and HRQoL

	Breztri versus	
Outcome	GLY/FOR	BUD/FOR
Rescue medication, over 52 weeks		
Percentage of rescue-free days, mean between-treatment difference	2.83 to 4.98; *P* ≤ .01	2.19 to 4.34; *P* ≤ .04
Puffs per day, mean between-treatment difference	−0.34 to −0.53; *P* < .001	−0.35; *P* < .001
HRQoL, at 52 weeks		
SGRQ total score mean between-treatment difference	−1.34 to −1.59; *P* < .001	−1.06 to −1.31; *P* ≤ .002
Time to clinically important deterioration[a]	OR, 1.42 to 1.46; *P* < .001	OR, 1.24 to 1.27; *P* < .001

Note. Shaded boxes indicate statistically significant findings. [a] Clinically important deterioration defined as an increase of ≥ 4 points from baseline.
Abbreviations. BUD: budesonide; FOR: formoterol; GLY: glycopyrrolate; HRQoL: health-related quality of life; N/A: not applicable; OR: odds ratio.

COPD Findings: Characteristics of Included Trelegy RCTs

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Study Study Duration Risk of Bias	N Randomized Participant Characteristics	Treatments
Bansal, 2021 12 weeks Moderate	• N = 800 • Moderate-to-severe COPD • Mean age: 66.2 years (SD, 7.9) • Male: 543 (68%) • Current smoker: 381 (48%)	• Trelegy (FLU/UMEC/VI) ○ 100/62.5/25 µg, n = 400 • TIO 18 µg, n = 400

Ferguson, 2020
12 weeks
Moderate
	• N = 1,461
	• COPD severity, NR
	• Mean age: 65.2 years (SD, 8.1)
	• Male: 758 (51.9%)
	• Current smoker: 714 (48.9%)
		• Trelegy (FLU/UMEC/VI)
		  ○ 100/62.5/25 µg, n = 729
		• BUD/FOR+TIO
		  ○ 400/12 + 18 µg, n = 731

FULFIL
24 weeks (up to 52 weeks)
Moderate
	• N = 1,810
	• COPD severity, NR
	• Mean age: 63.9 years (SD, 8.6)
	• Male: 1,341 (74.1%)
	• Current smoker: 794 (43.9%)
		• Trelegy (FLU/UMEC/VI)
		  ○ 100/62.5/25 µg, n = 911
		• BUD/FOR
		  ○ 400/12 µg, n = 899

Abbreviations. BUD: budesonide; COPD: chronic obstructive pulmonary disease; FOR: formoterol; FLU: fluticasone; NR: not reported; SD: standard deviation; TIO: tiotropium; UMEC: umeclidinium; VI: vilanterol.

COPD Findings: Characteristics of Included Trelegy RCTs

Study Study Duration Risk of Bias	N Randomized Participant Characteristics	Treatments

Bremner, 2018
24 weeks
High
	• N = 1,055
	• Moderate-to-severe COPD
	• Mean age: 66.3 years (SD, 8.6)
	• Male: 785 (74.4%)
	• Current smoker: 401 (38.0%)
		• Trelegy (FLU/UMEC/VI)
		  ○ 100/62.5/25 µg, n = 527
		• FLU/VI+UMEC
		  ○ 100/25 + 62.5 µg, n = 528

IMPACT 52 weeks High	• N = 10,355 • Moderate-to-severe COPD • Mean age: 65.3 years (SD, 8.3) • Male: 6,870 (66.3%) • Current smoker: 3,587 (34.6%)	• Trelegy (FLU/UMEC/VI) ○ 100/62.5/25 µg, n = 4,151 • FLU/VI (100/25 µg), n = 4,134 • UMEC/VI (62.5/25 µg), n = 2,070
INTREPID 24 weeks High	• N = 3,109 • Moderate-to-severe COPD • Mean age: 67.8 years (SD, 8.7) • Male: 1,655 (53.5%) • Current smoker, NR	• Trelegy (FLU/UMEC/VI) ○ 100/62.5/25 µg, n = 1,545 • Any MITT, n = 1,547

Abbreviations. COPD: chronic obstructive pulmonary disease; FLU: fluticasone; MITT: multi-inhaler triple therapy; NR: not reported; SD: standard deviation; UMEC: umeclidinium; VI: vilanterol.

COPD Findings: Trelegy vs. BUD/FOR with or without TIO Lung Function and Exacerbations

Outcome	Trelegy	Trelegy versus		
		TIO (12 weeks)	BUD/FOR+TIO (12 weeks)	BUD/FOR
Lung Function				
Trough FEV_1, mean CFB	32 to 142 ml	NR	−24 ml	−29 ml
Trough FEV_1, mean between-treatment difference	N/A	87 ml; *P* < .001	56 ml; *P*, NR	• Week 24: 171 ml; *P* < .001 • Week 52: 179 ml; *P* < .001
Trough FEV_1, responder rate	N/A	NR	NR	• Week 24: OR, 4.03; *P* < .001 • Week 52: OR, 4.79; *P* < .001
Exacerbations				
Annualized rate of moderate-to-severe exacerbations, rate ratio	N/A	NR	NR	• Week 24: 0.65; *P* = .002 • Week 52: 0.56; *P* = .006

Note. Shaded boxes indicate statistically significant findings.
Abbreviations. BUD: budesonide; CFB: change from baseline; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; FOR: formoterol; N/A: not applicable; NR: not reported; TIO: tiotropium.

COPD Findings: Trelegy vs. BUD/FOR with or without TIO Rescue Medication and HRQoL

	Trelegy versus		
Outcome	TIO (12 weeks)	BUD/FOR+TIO (12 weeks)	BUD/FOR
Rescue Medication			
Puffs per day, mean	NR	NR	NR
Puffs per day, mean between-treatment difference	NR	NR	• Week 24: −0.2; *P* < .001 • Week 52: −0.2; *P* = .02
HRQoL			
SGRQ total score mean between-treatment difference	−3.2; *P* < .001	0.0; *P* = .9	• Week 24: −2.2; *P* < .001 • Week 52: −2.7; *P* = .06
SGRQ, responder rate	OR, 1.62; *P* = .001	OR, 1.05; *P* = .7	• Week 24: OR, 1.41; *P* < .001 • Week 52: OR, 1.50; *P* = .05
CAT total score mean between-treatment difference	−1.2; *P* = .001	−0.3; *P* = .2	• Week 24: −0.9; *P* < .001 • Week 52: Details, NR; *P* ≥ .05
CAT, responder rate	OR, 1.15; *P* = .3	OR, 1.04; *P* = .7	• OR, 1.44; *P* < .001 • OR, 1.50; *P* = .048

Note. Shaded boxes indicate statistically significant findings.
Abbreviations. BUD: budesonide; CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; FOR: formoterol; N/A: not applicable; NR: not reported; OR: odds ratio; SGRQ: St. George's Respiratory Questionnaire; TIO: tiotropium.

COPD Findings: Trelegy vs. FLU/VI, UMEC/VI, or MITT Lung Function and Exacerbations

	Trelegy versus		
Outcome	FLU/VI (at 52 weeks)	UMEC/VI (at 52 weeks)	MITT (at 24 weeks)
Lung Function			
Trough FEV_1, mean between-treatment difference	97 ml; *P* < .001	54 ml; *P* < .001	26 to 53 ml; mixed results
Trough FEV_1, responder rate	NR	NR	NR
Exacerbations			
Annualized rate of moderate-to-severe exacerbations, rate ratio	0.85; *P* < .001	0.75; *P* < .001	NR
Time-to-first moderate-to-severe exacerbation	HR, 0.85; *P* < .001	HR, 0.84; *P* < .001	HR, 0.87; *P* ≥ .05

Note. Shaded boxes indicate statistically significant findings.
Abbreviations. COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; FLU: fluticasone; HR: hazard ratio; MITT: multi-inhaler triple therapy; N/A: not applicable; NR: not reported; SD: standard deviation; UMEC: umeclidinium; VI: vilanterol.

COPD Findings: Trelegy vs. FLU/VI, UMEC/VI, or MITT Rescue Medication and HRQoL

	Trelegy versus		
Outcome	FLU/VI (at 52 weeks)	UMEC/VI (at 52 weeks)	MITT (at 24 weeks)
Rescue medication			
Percentage of rescue-free days, mean between-treatment difference	5.2%; *P* < .001	4.4%; *P* < .001	NR
HRQoL			
SGRQ total score mean between-treatment difference	−1.8; *P* < .001	−1.8; *P* < .001	−0.9; *P* ≥ .05
SGRQ, responder rate	OR, 1.41; *P* < .001	OR, 1.41; *P* < .001	OR, 0.92; *P* ≥ .05
CAT total score mean between-treatment difference	NR	NR	NR
CAT, responder rate	OR, 1.24; *P* < .001	OR, 1.28; *P* < .001	OR, 1.31; *P* < .001

Note. Shaded boxes indicate statistically significant findings.
Abbreviations. CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; FLU: fluticasone; HR: hazard ratio; MITT: multi-inhaler triple therapy; N/A: not applicable; NR: not reported; SD: standard deviation; SGRQ: St. George's Respiratory Questionnaire; UMEC: umeclidinium; VI: vilanterol.

COPD Findings: Characteristics of Included Trimbow RCTs

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Study Name Study Duration Risk of Bias	N Randomized Participant Characteristics	Treatments

TRINITY
52 weeks
Moderate
	• N = 2,691
	• COPD severity, NR
	• Mean age: 63.2 (SD, 8.6)
	• Male: 2,056 (76.4%)
	• Current smoker: 1,286 (47.8%)
	• White: 2,670 (99.2%)
		• Trimbow (BDP/FOR/GLY)
		  ○ 100/6/12.5 µg, n = 1,078
		• TIO only (18 µg), n = 1,075
		• BDP/FOR+TIO
		  ○ (100/6 + 18 µg), n = 538

TRIVERSYTI 24 weeks Moderate	• N = 708 • COPD severity, NR • Mean age: 65.9 (SD, 7.4) • Male: 673 (95.0%) • Current smoker: 174 (24.5%) • East Asian: 708 (100%)	• Trimbow (100/6/10 µg), n = 353 • BUD/FOR (160/4.5 µg), n = 355

Abbreviations. BDP: beclomethasone dipropionate; BUD: budesonide; COPD: chronic obstructive pulmonary disease; FOR: formoterol; GLY: glycopyrrolate; NR: not reported; SD: standard deviation; TIO: tiotropium.

COPD Findings: Trimbow, Lung Function and Exacerbations

Outcome	Trimbow	Trimbow versus TIO (at 52 weeks)	Trimbow versus BUD/FOR+TIO (at 52 weeks)	Trimbow versus BUD/FOR (at 24 weeks)
Lung Function				
Trough FEV_1, mean CFB	80 ml	22 ml	91 ml	NR
Trough FEV_1, mean between-treatment difference	N/A	58 ml; *P* < .001	−11 ml; *P* = .3	70 ml; *P* < .001
Trough FEV_1, responder rate	N/A	OR, 1.62; *P* < .001	OR, 0.95; *P* = .6	OR, 2.58; *P* < .001
Exacerbations				
Annualized rate of moderate-to-severe exacerbations, rate ratio	N/A	0.80; *P* = .002	1.01; *P* = .9	0.57; *P* < .001
Time-to-first moderate-to-severe exacerbation	N/A	HR, 0.84; *P* = .01	HR, 1.06; *P* = .6	HR, 0.55; *P* < .001

Note. Shaded boxes indicate statistically significant findings.
Abbreviations. BUD: budesonide; CFB: change from baseline; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; FOR: formoterol; HR: hazard ratio; N/A: not applicable; OR: odds ratio; TIO: tiotropium.

COPD Findings: Trimbow, Rescue Medication, and HRQoL

	Trimbow versus		
Outcome	TIO (at 52 weeks)	BUD/FOR+TIO (at 52 weeks)	BUD/FOR (at 24 weeks)
Rescue medication			
Percentage of rescue-free days, mean between-treatment difference	8.78; *P* < .001	−1.24; *P* = .51	0.57; *P* < .001
Puffs per day, mean between-treatment difference	−0.61; *P* < .001	0.05; *P* = .6	−0.15; *P* < .001
HRQoL			
SGRQ total score mean between-treatment difference	NR	NR	−3.18; *P* < .001
Responder rate	OR, 1.33; *P* = .002	OR, 0.91; *P* = .4	NR

Note. Shaded boxes indicate statistically significant findings.
Abbreviations. BUD: budesonide; COPD: chronic obstructive pulmonary disease; FOR: formoterol; HRQoL: health-related quality of life; NR: not reported; OR: odds ratio; SGRQ: St. George's Respiratory Questionnaire; TIO: tiotropium.

Ongoing Studies

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Comparators	Condition	Age Range	Estimated Enrollment	Estimated Completion Date
Breztri vs. BUD/FOR	Asthma	12 to 80	4,400	January/March 2024[a]
Trelegy vs. FLU/VI	Asthma	≥ 18	288	September 2024
Trimbow+ SOC vs. SOC	COPD	> 18	200	February 2023
Trimbow vs. BDP/FOR	COPD	≥ 40	2,934	July 2024
Trimbow vs. Qvar + Bevespi	COPD	≥ 40	300	September 2024
Trimbow vs. SOC	COPD	≥ 40	316	Unclear (registered December 2019)

Note. [a] *Two replicate studies.*
Abbreviations. BDP: beclomethasone dipropionate; BUD: budesonide; FLU: fluticasone; FOR: formoterol; COPD: chronic obstructive pulmonary disease; SOC: standard of care; VI: vilanterol.

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Discussion

OHSU

Discussion: Summary

- Generally, SITTs demonstrated improvements in:
  - Lung function (i.e., trough FEV_1)
  - Frequency of moderate-to-severe exacerbations
  - Delay in time-to-first moderate or severe exacerbations
  - Frequency and volume of rescue medication use
  - HRQoL
- Non-inferiority compared with MITTs
- Rate and type of AEs, SAEs, and AEs of special interest (e.g., pneumonia) were similar among all treatments
- Early withdrawals due to AEs and deaths were rare

Discussion: Summary, SITTs vs. BUD/FOR

- For treatment of COPD, SITTs performed significantly substantially better than BUD/FOR

SITT	BUD/FOR
Breztri	• 20% less likely to experience FEV_1 deterioration (decrease ≥ 100 ml) • 25% more likely to increase SGRQ ≥ 4 points
Trelegy	• FEV_1 mean between-group difference of 170 to 180 ml • 4 to 5 times more likely to increase FEV_1 by ≥ 100 ml • Experience half the rate of exacerbations • 40% to 50% more likely to increase HRQoL scores to meet MCIDs
Trimbow	• 2.6 times more likely to increase trough FEV_1 by ≥ 100 ml • 45% delay in time to first moderate or severe exacerbation • Larger improvements in SGRQ scores

Abbreviations. BUD: budesonide; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; FOR: formoterol; HRQoL: health-related quality of life; MCID: minimal clinically important difference; SGRQ: St. George's Respiratory Questionnaire; SITT: single-inhaler triple therapy.

Discussion: Limitations of This Report

- Some outcomes of interest were rarely reported (e.g., hospitalizations, emergency visits)
- Subgroups of interest often excluded because of post-hoc analysis
- Rapid review, so no certainty of evidence or meta-analysis
- Treatment adherence not investigated by included studies, nor was it an outcome of interest, but this may be an important aspect to consider

State Considerations

- Medicaid population has higher proportions of asthma and COPD vs. private insurers
  - More severe disease with less management due to barriers (e.g., costs, access to services)
- SITTs can result in positive impacts, including adherence and persistence
  - Consistent treatment can impact:
    - Condition (i.e., asthma or COPD)
    - Outcomes for comorbid conditions
    - Health care utilization

State Considerations

- Consider individual patient profile (e.g., disease severity, treatment adherence)
  - Patient preferred outcomes (e.g., improvements in daily symptoms may be more important than reduction in exacerbations)
- Review benchmark document and other materials from American Lung Association Asthma Guidelines-Based Care Coverage Project
  - Provides information on key aspects of management
  - Addresses treatment barriers, particularly for Medicaid population
- Revisit National Heart, Lung, and Blood Institute documents
  - National plan for COPD (updated in 2019)
  - Asthma management guidelines (updated in 2020)

Questions?


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