Clinical Interpretation of Efficacy Outcomes in Pharmacological Studies on Triple Fixed-Dose Combination Therapy for Uncontrolled Asthma: Assessment of IRIDIUM and ARGON Studies

Paola Rogliani 1
Luigino Calzetta 2

1Unit of Respiratory Medicine, Department of Experimental Medicine, University of Rome “Tor Vergata”, Rome, Italy; 2Department of Medicine and Surgery, Respiratory Disease and Lung Function Unit, University of Parma, Parma, Italy

Abstract: The IRIDIUM and ARGON studies provided positive findings concerning the benefits of the once-daily triple mometasone furoate/indacaterol/glycopyrronium (MF/IND/GLY) fixed-dose combination (FDC) for the treatment of uncontrolled asthma, at the least by a strict statistical point of view. In the IRIDIUM study patients received medium-dose (MD) or high-dose (HD) MF/IND/GLY or MF/IND once daily or HD fluticasone/salmeterol (FLU/SAL) twice daily; in the ARGON study patients received MD or HD MF/IND/GLY once daily or HD FLU/SAL twice daily + tiotropium (TIO) once daily. Since a detailed interpretation of clinical results has not yet been performed, we provided the clinical interpretation of efficacy outcomes resulting from the IRIDIUM and ARGON studies according to the currently available minimal clinically important difference (MCID) thresholds. The triple MF/IND/GLY FDC elicited beneficial clinically relevant effects compared to active comparators in asthmatic patients, according to the levels of ICS doses, by generally achieving and overcoming the MCID. The level of clinical benefit was usually greater in patients treated with HD-MF/IND/GLY compared to those treated with MD-MF/IND/GLY. Overall, HD-MF/IND/GLY induced greater clinically relevant benefits even when compared to HD-FLU/SAL + TIO. Considering that a balanced triple MF/IND/GLY FDC with MD ICS resulted as effective as HD-MF/IND in preventing moderate or severe exacerbations, thus triple ICS/LABA/LAMA FDCs with MD ICS should be considered for the treatment not only of uncontrolled asthma but also for those patients suffering from less severe forms of disease with airflow limitation as well as a possible as-needed therapeutic option.

Keywords: ARGON study, IRIDIUM study, minimal clinically important difference, MCID, triple therapy, uncontrolled asthma

Background
The interpretation of findings obtained from randomized controlled trials (RCTs) is traditionally based on the statistical significance of results rather than clinical relevance, usually reported as the minimal clinically important difference (MCID). 1 The concept of MCID in RCTs has been known for a long time, and it can be defined as the smallest treatment effect that patients perceive as beneficial and which would mandate, in the absence of serious adverse events and excessive cost, a change in the patient’s management. 2 In this regard, it has been shown that in papers reporting data from pharmacological RCTs the clinical importance of...
results is often not adequately discussed or the authors do not provide sufficient information to allow readers make-
ing their own interpretation.¹

The P value is probably a statistical concept associated
with most fallacies and misuses in pharmacological stu-
dies, as a common misconception is that in positive RCTs
the outcome simply needs to be statistically significant.³
Along with statistically significance testing, the investi-
gated outcome requires careful interpretation of their
potential clinical impact.

The once-daily inhaled corticosteroid/long-acting β-
agonist/long-acting muscarinic antagonist (ICS/LABA/
LAMA) fixed-dose combination (FDC) mometasone furo-
ate/indacaterol/glycopyrronium (MF/IND/GLY) has been
recently approved for the treatment of asthma. The current
Global Initiative for Asthma (GINA, 2021)⁴ document
recommends to use this triple FDC as controller option
at asthma Step 4 and as preferred treatment at asthma Step
5 in adults and adolescents according to the positive
results and significant benefits for patients resulting from
the Phase III RCTs IRIDIUM⁵ and ARGON.⁶

In the IRIDIUM study,⁵ patients with inadequately
controlled asthma received medium-dose (MD) or high-
dose (HD) MF/IND/GLY or MF/IND once daily or HD
fluticasone/salmeterol (FLU/SAL) twice daily. In the
ARGON study,⁶ patients with uncontrolled asthma
received MD or HD MF/IND/GLY once daily or HD
FLU/SAL twice daily + tiotropium (TIO) once daily. The
level of ICS doses (MD and HF) included in the combina-
tions is ranked according to the current GINA
recommendations⁴ and the National Institute for Health
and Care Excellence (NICE)⁷ guidelines.

Although both these studies provided positive findings
at the least by a statistical point of view,⁶,⁸ to date a
detailed interpretation of clinical results has not yet been
performed. Therefore, here we provide the clinical inter-
pretation of efficacy outcomes resulting from the
IRIDIUM⁵ and ARGON⁶ studies according to the current-
ly available MCIDs.

### Spirometry

#### FEV₁

Clinical studies in asthmatic patients often include forced
expiratory volume in 1 s (FEV₁) as a primary outcome
since it has been generally recognized by research com-
munity and regulatory agencies to be a suitable variable to
assess airflow obstruction.⁹ The current standards of
MCID threshold for FEV₁ have been proposed for com-
parisons vs. placebo or for improvements vs. baseline,⁹-¹²
but difficulty still remains in evaluating the clinical sig-
nificance of spirometric outcomes when comparing either
active treatments or drugs administered as triple FDCs vs.
the same agents administered as dual FDCs.¹³ Therefore,
when assessing FEV₁ in chronic obstructive respiratory
disorders, it has been suggested a threshold MCID value
of >100 mL for trough FEV₁ for comparisons between
active treatments and either placebo or baseline,¹⁰,¹²
whereas the level of MCID threshold should be >60 mL
for trough FEV₁ when active treatments are compared to
each other.¹³

In the IRIDIUM study,⁵ MD-MF/IND/GLY significantly
improved trough forced FEV₁ by 76 mL (95% CI
41–111) vs. MD-MF/IND (P<0.001) and HD-MF/IND/
GLY significantly improved trough FEV₁ by 65 mL
(95% CI 31–99) vs. HD-MF/IND (P<0.001). Similarly,
MD-MF/IND/GLY significantly improved trough FEV₁
by 99 mL (95% CI 64–133) vs. HD-FLU/SAL (P<0.001)
and HD-MF/IND/GLY significantly improved trough
FEV₁ by 119 mL (95% CI 85–154) vs. HD-FLU/SAL
(P<0.001). MF/IND/GLY administered at both ICS doses
reached and overcame the MCID for trough FEV₁ when
comparing active treatments (MCID >60 mL). Of note,
when MF/IND/GLY was compared to HD-FLU/SAL, the
triple FDC reached the MCID for trough FEV₁ with
respect to placebo or baseline (MCID >100 mL).

In the ARGON study,⁶ HD-MF/IND/GLY significantly
improved trough FEV₁ by 96 mL (95% CI 46–146) vs.
HD-FLU/SAL + TIO (P<0.001), and it reached and over-
came the MCID for trough FEV₁ when compared to active
treatments (MCID >60 mL).

#### PEF

To date, no studies report a certain MCID threshold for
peak expiratory flow (PEF),¹⁴ however a minimal patient
perceivable improvement (MPPI) value of 5.39% has been
proposed for PEF as difference between active treatment
groups.¹²

In the ARGON study,⁶ HD-MF/IND/GLY significantly
(P<0.01) improved morning PEF vs. HD-FLU/SAL + TIO
(35.85 L/min vs 26.29 L/min); the absolute treatment
difference was 9.56 L/min (95% CI 2.89–6.29) and the
percentage treatment difference was 26.67%. HD-MF/
IND/GLY also significantly (P<0.01) improved evening
PEF vs. HD-FLU/SAL + TIO (31.86 L/min and 22.71 L/
min); the absolute treatment difference was 9.15 L/min
(95% CI 2.57–15.72) and the percentage treatment difference was 28.72%. Thus, it seems that HD-MF/IND/GLY reached and overcame the MPPI for PEF when compared to HD-FLU/SAL + TIO.

**Exacerbations**

Exacerbations have negative impact on quality of life of asthmatic patients. Since severe exacerbations may represent life-threatening events, preventing even a single episode could be considered a minimal clinically important improvement. In any case, the MCID threshold for severe asthma exacerbations has been identified as a reduction >20% in annual exacerbation rate.9

In the IRIDIUM study,5 HD-MF/IND/GLY significantly (P≤0.05) reduced the risk of all exacerbations (mild, moderate, and severe) and severe exacerbations vs. HD-MF/IND (rate ratio: 0.79 [95% CI 0.66–0.96] and 0.78 [95% CI 0.61–1.00], respectively) by reaching and overcoming the MCID for exacerbations (−21% and −22%, respectively). When compared to HD-FLU/SAL, HD-MF/IND/GLY significantly (P<0.001) reduced in a clinically relevant manner the risk of moderate or severe exacerbations (rate ratio: 0.64 [95% CI 0.52–0.78]; percentage reduction: −36%), severe exacerbations (rate ratio: 0.58 [95% CI 0.45–0.73]; percentage reduction: −42%), and all exacerbations (mild, moderate, and severe; rate ratio: 0.60 [95% CI 0.50–0.72]; percentage reduction: −40%). MD-MF/IND/GLY reduced in a significant (P<0.001) and clinically relevant manner vs. HD-FLU/SAL the risk of all exacerbations (mild, moderate, and severe; rate ratio: 0.70 [95% CI 0.58–0.84]; percentage reduction: −30%); MD-MF/IND/GLY also significantly reduced (P<0.05) the risk of moderate or severe exacerbations (rate ratio: 0.81 [95% CI 0.66–0.99]) vs. HD-FLU/SAL, but the percentage of reduction (−19%) was borderline with the MCID for exacerbations.

In the ARGON study,6 the effect of HD-MF/IND/GLY on ACQ-7 was significantly (P<0.01) greater than that elicited by HD-FLU/SAL + TIO (delta effect: −0.12 [95% CI −0.22 − −0.03]), and MF/IND/GLY administered at both ICS doses reached and reduced more than two-fold the MCID for ACQ-7 vs. baseline (MD-MF/IND/GLY: −0.08; HD-MF/IND/GLY: −0.09).

**AQLQ**

The MCID for Quality of Life Questionnaire (AQLQ) has been determined to be a cut point of 0.5.9,14

In the ARGON study,6 a significantly (P<0.05) greater proportion of patients treated with HD-MF/IND/GLY achieved the MCID for AQLQ vs. HD-FLU/SAL + TIO (+8.1%). Moreover, MF/IND/GLY administered at both ICS doses reached and overcome the MCID for AQLQ vs. baseline (MD-MF/IND/GLY: +8.1; HD-MF/IND/GLY: +8.17).

**SGRQ**

The MCID for St. George’s Respiratory Questionnaire (SGRQ) corresponds to a decrease of >4 points.9

In the ARGON study,6 the effect of HD-MF/IND/GLY on SGRQ was significantly (P<0.05) greater than that elicited by HD-FLU/SAL + TIO (delta effect: −2.00 [95% CI −3.90 − −0.09]). Moreover, MF/IND/GLY administered at both ICS doses reached and reduced around three-fold the MCID for SGRQ vs. baseline (MD-MF/IND/GLY: −11.95; HD-MF/IND/GLY: −13.29).

**Conclusion**

The assessment of efficacy outcomes reported in the IRIDIUM5 and ARGON6 studies indicates that the triple MF/IND/GLY FDC elicits beneficial clinically relevant effects compared to active comparators in asthmatic patients, according to the levels of ICS doses as shown in Table 1, where the dose of MF was increased from 80 μg to 160 μg. As expected, the level of clinical benefit...
was generally greater in patients treated with HD-MF/IND/GLY compared to those treated with MD-MF/IND/GLY. Interestingly, the current evidence indicates that HD-MF/IND/GLY induced greater clinically relevant benefits on FEV\textsubscript{1}, PEF, moderate exacerbations and AQLQ even when compared to HD-FLU/SAL + TIO, a free triple combination therapy including an ICS administered at high dose. However, according to the taxonomy suggested by Jones\textsuperscript{15} to rank the impact of treatments on SGRQ, the beneficial effect of HD-MF/IND/GLY on SGRQ was statistically but not clinically significant when compared to HD-FLU/SAL + TIO.

Indeed, these data fully support the position of the European Medicine Agency (EMA) reported in the “Human Medicines Highlights 2020” document, which included the triple MF/IND/GLY FDC (Enerzair Breezhaler) among a selection of medicines approved in 2020, and the only one in the therapeutic area of respiratory medicine, that represents an outstanding contribution to public health.\textsuperscript{16} Certainly, as stated in the EMA document,\textsuperscript{16} the authorisation of new medicines such as the triple MF/IND/GLY FDC is essential to advancing public health as it brings new opportunities to treat patients with uncontrolled asthma.

### Table 1: Clinical effect of MF/IND/GLY FDC administered at different ICS doses compared to active comparators on efficacy outcomes in asthmatic patients as reported in the IRIDIUM\textsuperscript{5} and ARGON\textsuperscript{6} studies

| Outcome                        | Treatment                  | Active comparator          | Delta  | Suggested MCID | Beneficial clinically relevant effect |
|--------------------------------|----------------------------|----------------------------|--------|----------------|---------------------------------------|
| FEV\textsubscript{1}           | MD-MF/IND/GLY              | MD-MF/IND                   | 76 mL  | >60 mL\textsuperscript{*} | Yes                                   |
|                                | MD-MF/IND/GLY              | HD-FLU/SAL                  | 99 mL  | Yes            | Yes                                   |
|                                | HD-MF/IND/GLY              | HD-MF/IND                   | 65 mL  | Yes            | Yes                                   |
|                                | HD-MF/IND/GLY              | HD-FLU/SAL                  | 119 mL | Yes            | Yes                                   |
|                                | HD-MF/IND/GLY              | HD-FLU/SAL + TIO            | 96 mL  | Yes            | Yes                                   |
| Morning PEF                    | HD-MF/IND/GLY              | HD-FLU/SAL + TIO            | 26.67% | >5.39%\textsuperscript{**} | Yes                                   |
| Evening PEF                    | HD-MF/IND/GLY              | HD-FLU/SAL + TIO            | 28.72% | Yes            | Yes                                   |
| All exacerbations (mild, moderate, and severe) | MD-MF/IND/GLY              | HD-FLU/SAL                  | -30%   | >-20%          | Yes                                   |
|                                | HD-MF/IND/GLY              | HD-MF/IND                   | -21%   | Yes            | Yes                                   |
|                                | HD-MF/IND/GLY              | HD-FLU/SAL                  | -40%   | Yes            | Yes                                   |
| Moderate or severe exacerbations | MD-MF/IND/GLY              | HD-FLU/SAL                  | -19%   | Borderline     | Yes                                   |
|                                | HD-MF/IND/GLY              | HD-FLU/SAL                  | -36%   | Yes            | Yes                                   |
| Moderate exacerbations         | HD-MF/IND/GLY              | HD-FLU/SAL + TIO            | -43%   | Yes            | Yes                                   |
| Severe exacerbations           | HD-MF/IND/GLY              | HD-MF/IND                   | -22%   | Yes            | Yes                                   |
|                                | HD-MF/IND/GLY              | HD-FLU/SAL                  | -42%   | Yes            | Yes                                   |
| ACQ-7                          | HD-MF/IND/GLY              | HD-FLU/SAL                  | +8.2% responders | >0.5 points | A greater proportion of patients achieved the MCID |
| AQLQ                           | HD-MF/IND/GLY              | HD-FLU/SAL + TIO            | +8.1% responders | >0.5 points | A greater proportion of patients achieved the MCID |
| SGRQ                           | HD-MF/IND/GLY              | HD-FLU/SAL + TIO            | -2.00  | >4 units       | No                                    |

*Notes: * vs. active treatment. **Assessed via MPPI.

*Abbreviations:* ACQ-7, Asthma Control Questionnaire 7; AQLQ, Quality of Life Questionnaire; FEV\textsubscript{1}, forced expiratory volume in 1 s; FDC, fixed-dose combination; FLU, fluticasone; GLY, glycopyrronium; HD, high-dose; ICS, inhaled corticosteroid; IND, indacaterol; MD, medium-dose; MCID, minimal clinically important difference; MF, mometasone furoate; MPPI, minimal patient perceivable improvement; PEF, peak expiratory flow; SAL, salmeterol; SGRQ, St. George's Respiratory Questionnaire; TIO, tiotropium.
Finally, but not less important, a balanced triple MF/IND/GLY FDC with MD ICS resulted as effective as HD-MF/IND in preventing moderate or severe exacerbations, a phenomenon that was detected also against the increased contractile tone of human hypertensive bronchi and airway inflammation. Thus, triple ICS/LABA/LAMA FDCs with moderate ICS dose should be considered for the treatment not only of uncontrolled asthma but also for those patients suffering from less severe forms of disease with airflow limitation as well as a possible as-needed therapeutic option.

Disclosure
Professor Paola Rogliani reports grants, personal fees, non-financial support from Novartis, outside the submitted work. Dr Luigino Calzetta reports grants, personal fees from Novartis, outside the submitted work. The authors report no other conflicts of interest in this work.

References
1. Chan KBY, Man-Son-Hing M, Molnar FJ, et al. How well is the clinical importance of study results reported? An assessment of randomized controlled trials. Can Med Assoc J. 2001;165:1197.
2. Jaeschke R, Singer J, Guyatt GH. Measurement of health status: ascertaining the minimal clinically important difference. Control Clin Trials. 1989;10(4):407-415. doi:10.1016/0197-2456(89)9005-6
3. Calzetta L, Ritondo BL, Coppola A, et al. Factors influencing the efficacy of COVID-19 vaccines: a quantitative synthesis of Phase III trials. Vaccines. 2021;9:341. doi:10.3390/vaccines9040341
4. GINA. 2021 GINA main report | Global Initiative for Asthma [Internet]; 2021 [cited July 22, 2021]. Available from: https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf. Accessed December 29, 2021.
5. Kerstjens HAM, Maspero J, Chapman KR, et al. Once-daily, inhaled mometasone-indacaterol-glycopyrronium versus mometasone-indacaterol or twice-daily fluticasone-salmeterol in patients with inadequately controlled asthma (IRIDIUM): a randomised, double-blind, controlled Phase 3 study. Lancet Respir Med. 2020;8:1000–1012. doi:10.1016/S2213-2600(20)30190-9
6. Gessner C, Kornmann O, Maspero J, et al. Fixed-dose combination of indacaterol/glycopyrronium/mometasone furoate once-daily versus salmeterol/fluticasone twice-daily plus tiotropium once-daily in patients with uncontrolled asthma: a randomised, Phase IIIb, non-inferiority study (ARGON). Respir Med. 2020;170:106021. doi:10.1016/j.rmed.2020.106021
7. NICE. National Institute for Health and Care Excellence (NICE). Inhaled corticosteroid doses for NICE’s asthma guideline; 2018. Available from: www.nice.org.uk/guidance/ng80/resources/inhaled-corticosteroid-doses-pdf-4731528781. Accessed January 16, 2020.
8. Vichow JC. Assessing the benefits of triple versus dual fixed-dose combinations for the treatment of severe asthma. Lancet Respir Med. 2020;8:937–939. doi:10.1016/S2213-2600(20)30303-9
9. Bonini M, Di Paolo M, Bagnasco D, et al. Minimal clinically important difference for asthma endpoints: an expert consensus report. Eur Respir Rev. 2020;29:1–14. doi:10.1183/16000617.0137-2019
10. Parulekar A, Alobaidy A, Hanania N. Asthma outcomes revisited. Curr Opin Pulm Med. 2013;19:6–12. doi:10.1097/MCP.0b013e32835b118f
11. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26:948–968. doi:10.1183/09031936.05.0035205
12. Santanello N, Zhang J, Seidenberg B, et al. What are minimal important changes for asthma measures in a clinical trial? Eur Respir J. 1999;14:23–27. doi:10.1034/j.1399-3003.1999.14a06.x
13. Bateman E. Lack of clinically relevant differences between combination therapy and monotherapy in COPD. Eur Respir J. 2014;43:1204–1205. doi:10.1183/09031936.00156313
14. Validity of outcome measures; [cited July 20, 2021]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK409867/. Accessed December 29, 2021.
15. Jones PW. St. George’s respiratory questionnaire: MCID. Eur Respir J. 2005;2:75–79. doi:10.1183/09031936.00156313
16. Human medicines: highlights of 2020 | European Medicines Agency [Internet]; [cited July 20, 2021]. Available from: https://www.ema.europa.eu/en/news/human-medicines-highlights-2020. Accessed December 29, 2021.
17. Rogliani P, Ritondo BL, Facciolo F, et al. Indacaterol, glycopyrro- nium, and mometasone: pharmacological interaction and anti-inflammatory profile in hyperresponsive airways. Pharmacol Res. 2021;172:105801. doi:10.1016/j.phrs.2021.105801