The role of opicapone in the management of Parkinson’s disease: an Italian consensus through a combined Nominal Group Technique and Delphi approach

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Abstract. – OBJECTIVE: Opicapone (OPC) is a third-generation peripheral catechol-O-methyl transferase inhibitor (COMT-i) approved as add-on therapy to levodopa/DOPA decarboxylase inhibitors (DDCI) combinations in Parkinson’s disease (PD) patients with end-of-dose motor fluctuations. While the OPC effectiveness on motor symptoms is well known, there is still uncertainty about the timing of introduction, the management of levodopa dose, and the efficacy on non-motor symptoms (NMS).

SUBJECTS AND METHODS: A group of PD experts participated in a consensus activity composed of the Nominal Group Technique (NGT) and the Delphi method to better define the role of OPC. A list of statements was defined with the NGT and voted on through an online Delphi process by a panel of 85 Italian clinicians.

RESULTS: 24 statements were selected for the Delphi voting. Most statements (n=15, 62%) reached a consensus. A wide agreement was reached about the efficacy of OPC in treating motor fluctuations, including early morning akinesia and nocturnal akinesia. The panel widely agreed about the effectiveness of OPC in early fluctuating patients. The long-lasting inhibitory effect of OPC was recognized as an advantage over other COMT-i, resulting in a single daily dose and greater ease of introduction into the levodopa therapeutic regimen.

CONCLUSIONS: The efficacy of OPC observed in the clinical trials for the management of PD patients with motor fluctuations is also experienced in clinical practice. The review of the current positioning of OPC from the late to early stages of the disease may represent an important step in the evolution of the PD therapeutic approach.

Key Words: Parkinson’s disease, COMT inhibitor, Opicapone, Motor fluctuations.

Introduction

Levodopa opened a new era in treating Parkinson’s disease (PD) and is still considered the gold standard of PD therapy. Nevertheless, levodopa has a short half-life (60-90 min), which leads to
the occurrence of wearing-off fluctuations together with the loss of striatal dopamine nerve terminals (“OFF” periods)\(^3\). The management of motor fluctuations represents a major clinical need for people with PD, even in the early phases of the disease\(^6\-\^8\).

Opicapone (OPC) is a novel third-generation peripheral catechol-O-methyl transferase inhibitor (COMT-i). The European Medicine Agency approved its use in 2016 as an add-on therapy to combinations of levodopa/DOPA decarboxylase inhibitors (DDCI) in adult patients with PD who present with end-of-dose motor fluctuations\(^6\,^9\,^{10}\).

In the randomized, double-blind, placebo-controlled trials\(^1\,^{11}\,^{12}\) BIPARK I and BIPARK II, and in the open-label extensions of both BIPARK trials, the efficacy and safety of OPC were studied in over 1,000 PD patients with end-of-dose motor fluctuations. These studies showed that OPC could improve OFF- and ON-time in patients with recent onset of motor fluctuations and those at a more advanced stage. However, two subsequent post hoc analyses suggested that OPC shows an enhanced efficacy and more favorable tolerability profile in PD patients in earlier stages than in later stages. Indeed, PD patients in earlier stages disclosed a greater reduction in OFF-time and increased ON-time, and they had a lower incidence of dopaminergic-related adverse events, such as nausea, dyskinesia, orthostatic hypotension, and hallucinations\(^13\,^{14}\).

Real-world data from the prospective OPTIPARK study confirmed the effectiveness and tolerability of OPC observed in the pivotal trials\(^15\).

While most PD experts are aware of OPC’s effectiveness on motor symptoms, there is a need to know more about other aspects, such as the timing of introduction, the management of levodopa dose, and the efficacy on non-motor fluctuations (NMS)\(^6\,^{16}\). To address this issue, a group of neurologists with expertise in the management of PD started a consensus process to better define the role of OPC in the current therapeutic scenario of PD, sharing their real-life clinical experiences. In particular, a combined approach of two different consensus methods was used, namely the Nominal Group Technique (NGT) and the Delphi method. The combination of NGT and Delphi is a previously validated consensus approach and is increasingly used to provide a robust collection of expert opinions\(^17\,^{19}\). This paper presents and critically discusses the results of this consensus process.

Subjects and Methods

Project Overview

A working group composed of two coordinators and six PD experts (Scientific Board) participated in an online meeting to discuss the role of OPC in clinical practice and generate a list of statements on this topic through the NGT process. At the first meeting, the coordinators defined three key questions used to generate statements through the NGT round.

The statements defined at the end of the NGT process were included in the Delphi survey, which was submitted to the Scientific Board for testing and approval and then sent to the Delphi panel for voting. The Delphi panel was composed of 85 Italian neurologists who met at least two of the following criteria: ≥5 years of clinical experience in PD, ≥4 scientific publications in this field, and/or regular speaking activity at national/international congresses. The Delphi panel included the Scientific Board. With the exception of members of the Scientific Board, other panelists were not involved in the NGT process and did not receive any compensation. The vote was anonymous.

The Delphi survey was developed online using SurveyMonkey software. A timeline of 21 calendar days to answer was established. A further 7 days were granted after a reminder e-mail.

After the Delphi round, all the experts reviewed and discussed the outcomes during a second meeting (Figure 1). An unconditioned grant from BIAL Italia SRL (Milan, Italy) supported this project.

Key Questions

In the context of the NGT process, the formulation of ideas and statements is carried out according to some key questions posed to the participants. Within this project, the coordinators reviewed the most recent literature on OPC in PD therapy and drafted three key questions according to the following macro-areas of interest:

1. COMT and COMT-i: function and role of inhibitors in the motor fluctuations of patients with PD.
2. The role of OPC in PD therapy: perceived clinical effectiveness, safety, and tolerability.
3. Selection of patients with PD who may benefit most from OPC therapy.

NGT

The NGT is a direct and structured technique to manage organized meetings to make decisions...
and provide guidance on a specific topic not supported by robust literature evidence. In the context of this project, an adapted form of the NGT was used to generate a list of statements for the Delphi Panel. The adapted NGT involved a preliminary and individual preparation phase based on reviewing the most recent literature on the topics of interest. During the first meeting, the coordinators and each member of the Scientific Board shared thoughts and opinions on each of the identified key questions. All opinions were discussed, refined, and converted into statements. After the NGT session, the coordinators ranked the statements according to priority and relevance, defining the final list to be submitted to the Delphi Panel.

**Delphi Method**

The Delphi method is a standard method of consensus, which interactively and anonymously evaluates the level of agreement (consensus quantification) using a Likert scale (1-5; 1=total disagreement; 5=total agreement). Consensus on the agreement is reached when ≥75% of voters express a vote equal to 4 or 5. Within this project, the Delphi method was conducted through online voting.

**Statistical Analysis**

All data were analyzed with descriptive statistics.

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**Results**

**NGT Outcome**

During the NGT round, all the experts provided opinions on the three key questions and defined a list consisting of 42 statements. Coordinators defined a final list of 24 statements (four in the first macro-area, fifteen in the second macro-area, and five in the third macro-area) for the Delphi voting (Table I).

**Delphi Round**

During the online Delphi process, consensus on the agreement was reached for 15 out of 24 statements (62%; Table I, grey highlighted statements). The consensus was reached for two statements out of four from the macro-area 1 (M1-S1, M1-S2), eleven statements out of fifteen from the macro-area 2 (M2-S1, M2-S2, M2-S3, M2-S4, M2-S5, M2-S6, M2-S7, M2-S10, M2-S11, M2-S13, M2-S14) and two statements out of five from the macro-area 3 (M3-S1, M3-S2). The Delphi process was concluded in one round.

**Discussion**

OPC, a third-generation COMT-i, shows a long-lasting enzymatic inhibition and an improved safety profile compared with previous generations of COMT-i. Although the
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Table I. Results of Delphi panel.

<table>
<thead>
<tr>
<th>Statements (n = 24)</th>
<th>Consensus score (%)*</th>
<th>Responses (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(4+5) 1 2 3 4 5 1+2</td>
<td></td>
</tr>
<tr>
<td><strong>Macro area 1: COMT and COMT inhibitors: function and role of inhibitors in the motor fluctuations of patients with PD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. The administration of COMT inhibitors with levodopa and DDCI increases plasma levodopa bioavailability in patients with PD, improves levodopa pharmacokinetics, and reduces OFF-time.</td>
<td>96.5</td>
<td>1.2 0.0 2.4 28.2 68.2 1.2</td>
</tr>
<tr>
<td>2. When combined with levodopa/DDCI, COMT inhibitors re an effective treatment of fluctuations in PD</td>
<td>94.1</td>
<td>1.2 1.2 3.5 31.8 62.4 2.4</td>
</tr>
<tr>
<td>3. All COMT inhibitors used in PD retain similar efficacy</td>
<td>15.3</td>
<td>14.1 34.1 36.5 12.9 2.4 48.2</td>
</tr>
<tr>
<td>4. The application of standardized rating scales (e.g., WOQ-19) may help the early detection of fluctuations in patients with PD</td>
<td>69.4</td>
<td>1.2 3.5 25.9 45.9 23.5 4.7</td>
</tr>
</tbody>
</table>

| **Macro area 2: The role of opicapone in PD therapy: perceived clinical effectiveness, safety, and tolerability** |
| 1. Compared with other COMT inhibitors, opicapone has the advantage of a long inhibitory effect, which allows a single daily dose | 95.3 | 1.2 0.0 3.5 18.8 76.5 1.2 |
| 2. Opicapone reduces the OFF-time in fluctuating patients with PD | 98.8 | 0.0 0.0 1.2 36.5 62.4 0.0 |
| 3. Opicapone may improve early morning akinesia and nocturnal akinesia | 82.4 | 0.0 2.4 15.3 43.5 38.8 2.4 |
| 4. The effects of opicapone occur very early after the onset of the treatment | 75.3 | 0.0 4.7 20.0 47.1 28.2 4.7 |
| 5. The switch from entacapone to opicapone may be beneficial to patients | 82.4 | 0.0 4.7 12.9 52.9 29.4 4.7 |
| 6. The switch from entacapone to opicapone is rather simple and can be performed overnight | 89.4 | 0.0 2.4 8.2 40.0 49.4 2.4 |
| 7. It is easier to introduce opicapone into the current treatments than other COMT inhibitors | 77.6 | 1.2 5.9 15.3 30.6 47.1 7.1 |
| 8. Opicapone is more effective than entacapone on night-time akinesia | 70.6 | 1.2 5.9 22.4 44.7 25.9 7.1 |
| 9. Opicapone may improve non-motor symptoms | 58.8 | 0.0 9.4 31.8 43.5 15.3 9.4 |
| 10. Opicapone improves the quality of life | 89.4 | 0.0 2.4 8.2 71.8 17.6 2.4 |
| 11. Opicapone may be associated with MAO-B inhibitors | 95.3 | 0.0 1.2 3.5 45.9 49.4 1.2 |
| 12. The efficacy of opicapone is not dependent on the levodopa dose | 52.9 | 4.7 15.3 27.1 36.5 16.5 20.0 |
| 13. Levodopa dose adjustment can be necessary after the introduction of opicapone | 91.8 | 0.0 2.4 5.9 42.4 49.4 2.4 |
| 14. Introducing opicapone may induce hallucinations and confusion | 77.6 | 2.4 5.9 14.1 69.4 8.2 8.2 |
| 15. Long-term use of opicapone with modulation of levodopa dose is not associated with an increase in troublesome dyskinesia | 47.1 | 1.2 8.2 43.5 35.3 11.8 9.4 |

| **Macro area 3: Selection of patients with PD who may benefit most from opicapone therapy** |
| 1. Early fluctuators can be defined as patients suffering from wearing off for less than 1 year and taking three doses of levodopa a day | 80.0 | 2.4 4.7 12.9 55.3 24.7 7.1 |
| 2. Opicapone can be effective in early fluctuators | 89.4 | 0.0 2.4 8.2 57.6 31.8 2.4 |
| 3. Opicapone can represent the first add-on therapy in patients receiving levodopa | 54.1 | 2.4 16.5 27.1 36.5 17.6 18.8 |
| 4. Opicapone should not be used in patients taking more than five doses of levodopa a day | 9.4 | 29.4 32.9 28.2 4.7 4.7 62.4 |
| 5. Opicapone is equally effective in patients with or without dyskinesias | 40.0 | 3.5 27.1 29.4 29.4 10.6 30.6 |

*Consensus on the agreement is reached when ≥ 75% of voters express a vote equal to 4 or 5. The percentage reported in bold refers to the agreement of consensus. To facilitate the reading of the table, statements that reached consensus are grey colored. COMT: catechol-o-methyltransferase; DDCI: dopa decarboxylase inhibitor; MAO-B: monoamine oxidase type B; PD: Parkinson’s disease.
efficacy and safety of OPC have been proven in clinical trials, other aspects of the use of OPC in clinical practice particularly the timing of introduction, dose management of levodopa and its role in NMS management merit further elucidation. Therefore, while new clinical trials on the use of OPC are ongoing\(^2\), a consensus approach can help neurologists in positioning OPC in the PD therapeutic scenario.

Within this project, 24 statements were selected for the Delphi voting. Most of the statements (62%) reached a consensus during the Delphi round.

**Function and Role of COMT-i in the Management of Motor Fluctuations**

A high level of agreement (about 95%) was reported on the evidence that COMT-i represents an effective treatment of end-of-dose motor fluctuations in PD and that administration of COMT-i as add-on therapy to levodopa/DDCI increases plasma levodopa bioavailability, thus improving levodopa pharmacokinetics and reducing OFF-time (M1-S1, M1-S2). This is in line with previous literature and supports the beneficial role of COMT-i\(^2\), even though COMT-i is still the less-used therapeutic class in PD and is positioned late in the PD therapeutic algorithm in clinical practice\(^2\). However, the strategy of adding COMT-i to levodopa treatment to achieve a dual inhibition of main levodopa metabolic pathways is increasingly adopted, and the high level of agreement reached about COMT-i efficacy and early introduction of OPC confirms this pattern.

Most PD experts acknowledge that all COMT-i do not show the same efficacy; however, one-third of the panel was uncertain (M1-S3). This uncertainty may be due to a lack of long-term clinical experience with OPC or a lack of studies directly comparing the activity of different COMT-i. A recent network meta-analysis\(^2\) tried to shed light on this point, suggesting that OPC has intermediate effectiveness between tolcapone and entacapone in terms of patients’ total ON-time and it presents the lowest adverse event rates; still, these conclusions are based on statistical analysis only, and need confirmation in clinical studies.

The early detection of motor fluctuations is a relevant issue in enhancing the therapy effectiveness through better regimen adjustment, significantly improving patient quality of life (QoL), and gaining a deeper understanding of the evolution of the disease\(^2\). In this context, the panel did not reach an agreement on the usefulness of standardized rating scales for early detection of motor fluctuations (e.g., WOQ-19; M1-S4). Some resistance to using standardized rating scales in clinical practice was reported, mainly due to the limited time for follow up visits and the poor reliability of patient-reported assessments\(^2\,\text{and}^7\). The limitations of current methods could be overcome by the wider adoption of wearable devices, which can collect PD motor fluctuations objectively and reliably\(^2\,\text{and}^7\).

**The Role of OPC in PD Therapy**

A wide agreement on the effectiveness of OPC in reducing the OFF-time and improving early morning akinesia, nocturnal akinesia, and QoL was reported, further supporting the literature evidence (M2-S1, M2-S2, M2-S3, M2-S10)\(^3\,\text{and}^\text{12}\). The panel also agreed on the greater ease of introducing OPC into the PD therapeutic regimen compared with other COMT-i (M2-S6, M2-S7). Indeed, OPC is administered once daily, has a rapid onset of action, and does not generally require a change in levodopa formulation and daily intake frequency.

In BIPARK I study\(^1\), when tested for non-inferiority, a difference of -26.2 mins OFF-time was found in favor of OPC when compared with entacapone. Within the panel, a broad consensus was reached regarding the beneficial effect of the switch from entacapone to OPC (M2-S5). This is in line with literature evidence showing that switching from entacapone to OPC leads to further decreases in OFF-time\(^2\). No consensus was reported about the greater effectiveness of OPC on night-time akinesia compared with entacapone (M2-S8); however, post hoc analyses\(^2\,\text{and}^\text{12}\) of BIPARK I and II suggested that OPC can lead to greater improvement in the duration of overnight OFF-time and time to morning ON in comparison to entacapone.

About 30% of the panel was uncertain about the effectiveness of OPC in improving NMS (M2-S9). In the BIPARK II study, an improvement of the NMS scale was observed in favor of OPC for the sleep/fatigue domain, and no worsening of any domain, such as dysautonomia, hallucinations, or cognitive dysfunction, was observed. However, the NMS scale total score was not statistically different from the placebo\(^4\). More recently, the OPTIPARK study, conducted under clinical practice conditions, suggested the effectiveness of OPC on global NMS burden. The OPEN-PD prospective study suggested that OPC could improve the NMS globally (specifically in
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sleep, fatigue, mood, gastrointestinal symptoms, and pain) and QoL in PD patients at 6 months\textsuperscript{35,39}. Since the evaluation of NMS is an emerging topic in the context of PD treatment, additional studies are needed\textsuperscript{36}.

More than 75% of the panel agreed with the statement that OPC may induce hallucinations and/or confusion (M2-S14). These are well-known side effects of dopaminergic stimulation, with the most relevant risk factors being the patient’s age, cognitive impairment, disease duration, and high levodopa equivalent daily dose\textsuperscript{37-39}. Therefore, similar to other add-on therapies for PD, the prompt information and monitoring of at-risk subjects is advised; moreover, reducing dopaminergic therapy (in particular dopamine-agonists and night-time levodopa) is suggested in patients with cognitive impairment and/or experiencing hallucinations after OPC introduction. If necessary, low-dose atypical antipsychotics (clozapine, quetiapine) may be of benefit.

A consensus was not reached on the efficacy of OPC independently of levodopa dose (M2-S12), although sub-analyses\textsuperscript{3,40} of BIPARK I and II showed that OPC was efficacious for all levodopa intakes and daily amounts.

About 40% of the panel was uncertain about the association between long-term use of OPC and an increase in troublesome dyskinesia (M2-S15), even if the levodopa dose was adjusted. In both BIPARK I and BIPARK II studies, treatment with OPC was not associated with significant increases in ON-time with troublesome dyskinesia compared with placebo; the rate of troublesome dyskinesia remained consistently low during the 1-year open-label phase, with no relevant changes observed in the mean ON-time with troublesome dyskinesia\textsuperscript{21,41}.

It is interesting to notice that most of the experts (92%) agreed with the need for levodopa dose adjustment after OPC introduction (M2-S13); as discussed above, a reduction in levodopa equivalent daily dose can be necessary if patients experience dopaminergic-related adverse events after OPC introduction, which is more likely to happen in patients with advanced disease\textsuperscript{14}.

**PD Patients who May Benefit Most from OPC Therapy**

The panel widely agreed about the effectiveness of OPC in early fluctuating patients (M3-S2). The wide consensus confirms the results of BIPARK trials. The panel also suggests a revision of the current positioning of OPC from the late to early stages of the disease that could bring benefits for patients, as treatment with OPC allows optimization of the plasma levels of levodopa, providing a more continuous stimulation in comparison to levodopa only regimens or other add-on strategies.

About 30% of the panel was uncertain about the indication of OPC as the first add-on therapy in patients receiving levodopa (M3-S3). According to the Experts’ opinion, this might reflect the common practice of reserving OPC for patients with advanced disease due to being perceived as more potent than other add-on therapies. Another possible explanation for the lack of consensus could be the absence of indications for using COMT-i in patients without motor fluctuations. This may become clearer with the results of the ongoing trial EPSILON, which investigates the effect of OPC in PD patients with signs of motor disability but not end-of-dose motor fluctuations\textsuperscript{42}. In addition, early use of long-acting COMT-i is suggested by the latest AAN guidelines\textsuperscript{43}.

About 60% of the Experts disagreed that OPC should not be used in patients taking >5 doses of levodopa, while about one-third was uncertain (M3-S4). This uncertainty could be explained by the higher risk of developing dyskinesia in patients who are later in their disease course and levodopa treatment pathways. However, the efficacy and safety of OPC have also been proven in these patients, as shown in the post hoc analyses of BIPARK I and II trials\textsuperscript{3,44}. In particular, a post hoc analysis\textsuperscript{44} of the BIPARK I study showed that patients developing dyskinesia might benefit from early follow-up and reduced dopaminergic treatment, as dyskinesia mainly occurs in the first few weeks of OPC treatment and patients taking a high levodopa dose and concomitant dopamine agonists.

Lastly, a consensus was not reached about the equal effectiveness of OPC in patients with or without dyskinesias (M3-S5); however, a post hoc analysis\textsuperscript{43} from combined BIPARK-I and II showed that OPC is effective in reducing OFF-time and increasing ON-time regardless of the presence of dyskinesia at baseline.

**Limitations**

This study presents some limitations, as the consensus and study conclusions are panel-based, rather than evidence-based. Moreover, the panel was composed of Italian movement disorder specialists only, even though many of them have international expertise. However, the guiding
principles used for the statements’ definitions are based on solid scientific evidence, and the conclusions provided here may represent a further step in the evolution of the PD therapeutic approach.

Conclusions

A wide agreement was reached about the efficacy of OPC in treating motor fluctuations, including early morning akinesia and nocturnal akinesia. The panel also widely agreed about the effectiveness of OPC in early fluctuating patients, supporting the introduction of OPC in the early stages of motor fluctuations, as it could bring advantages related to improved levodopa plasma levels, which provide a more effective and continuous stimulation. An advantage of OPC over other COMT-i is the long-lasting inhibitory effect, resulting in a single daily dose and easier introduction into the levodopa therapeutic regimen.

Taken together, results suggest that the efficacy of OPC observed in the clinical trials for the management of PD patients with motor fluctuations is also experienced in clinical practice and that the revision of the current positioning of OPC from late to earlier stages of the disease may be beneficial for patients.

Conflict of Interest

Angelo Antonini has received compensation for consultancy and speaker-related activities from UCB, Boehringer Ingelheim, General Electric, Britannia, AbbVie, Kyowa Kirin, Zambon, Bial, Seravance BioPharma, Jazz Pharmaceuticals, Roche, Medscape; he receives research support from Bial, Lundbeck, Roche, Chiesi Pharmaceuticals, Angelini Pharmaceuticals, Horizon 2020 - Grant 825785, Horizon2020 Grant 101016902, Ministry of Education University and Research (MIUR) Grant ARS01_01081, Cariparo Foundation, Movement Disorders Society for NMS Scale validation. He serves as a consultant for Boehringer-Ingelheim for legal cases on pathological gambling. Paolo Barone: has received compensation for consultancy and/or speaker-related activities from UCB Pharma, AbbVie, Zambon, Biogen, Lusofarmaco, Bial, Roche, Chiesi, Lundbeck Paolo Calabresi received research support, speaker honoraria, and support to attend national and international conferences (not related to the present study) from Abbvie, Bial, Bayer Schering, Biogen-Dompé, Biogen-Idec, Eisai, Lilly, Lundbeck, Lusofarmaco, Merck-Serono, Novartis, Sanofi-Genzyme, Teva, UCB Pharma, Zambon. Prof. Lopiano received honoraria for lecturing and travel grants from Medtronic, UCB Pharma, AbbVie, Zambon, Bial, Lusofarmaco, Chiesi. Francesca Morgante: Speaking honoraria from Abbvie, Medtronic, Bial, Merz, Boston Scientific; Travel grants from the International Parkinson’s Disease and Movement Disorder Society; Advisory board fees from Merz, Abbvie, Boston Scientific; Consultancies fees from Boston Scientific, Merz and Bial; Research support from NIHR, Boston Scientific, Merz, and Global Kinetic; Royalties for the book “Disorders of Movement” from Springer. Francesco E. Pontieri has received compensation for consultancy and speaker-related activities from Abbvie, Bial, and Zambon; He has received research support from Lundbeck, Zambon, the Italian Ministry of University and Research, and the Italian Ministry of Health. Mariachiara Sensi: has received compensation for consultancy and speaker-related activities from Medtronic, Boston Scientific. Fabrizio Stocchi: LUNDBECK, UCB, Chiesi, Zambon, Britannia, Cynapsus, Sunovion, Kyowa, Abbvie, Neuroderm, Biogen, BIAL.

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Authors’ Contribution

All Authors contributed to the definition and contextualization of statements, critically edited the manuscript, and approved its final version for submission.

Data Availability

All data are available from the corresponding author upon reasonable request.
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