Summary of expert discussions and conclusions

Executive summary

Consensus Conference rationale

- A panel of twelve European (including UK and Israel) experts and key opinion leaders in pneumology and infectious diseases convened in Milan, Italy, on February 22nd-23rd for a consensus meeting. The focus of discussions was the ever more prevalent Non-Tuberculous Mycobacterial (NTM) lung infections caused by ubiquitous, free-living, environmental saprophytic, slow-growing *Mycobacterium avium* complex (MAC). Prof. Stefano Alberti, Professor of Respiratory Medicine at Humanitas University, Milan, Italy, was the Scientific Director of the Consensus Conference and had the steering leadership of the meeting. The convened Consensus Conference aimed at defining and clarifying ambiguities about the "Therapeutic Indications" in the EMA-approved ARIKAYCE liposomal *[Amikacin Liposome Inhalation Suspension, ALIS]* Summary of Product Characteristics valid in the EU, UK, and Israel. The EMA regulatory document states: *"…indicated for the treatment of NTM lung infections caused by MAC in adults with limited treatment options who do not have cystic fibrosis"*. The ambiguities focus on what exactly "limited treatment options" for MAC-PD *[MAC pulmonary disease]* means.

- A few other questions arise from the EMA "Therapeutic Indications" ambiguities: where should we draw the conceptual and operative boundaries for defining the MAC-PD "limited treatment options"? Is the official EMA expression too vague to ensure that all eligible MAC-PD patients could benefit from ARIKAYCE liposomal?

- The EMA definition diverges from the more straightforward "treatment-refractory MAC lung disease" indication for ARIKAYCE produced in September 2018 by the FDA. In the FDA definition, the pivot "refractory" concept stands for patients lacking culture conversion after at least six months of GBT therapy *[GBT: guideline-based, triple-drug regimen (ATS/ERS/ESCMID/IDSA clinical practice guidelines, Eur Respir J 2020; 56: 2000535. DOI:10.1183/13993003.00535-2020]*.

Preliminary activities in preparation for the Consensus Conference in Milan, Italy

- An **online literature review** was performed by a panel of experts from countries where ARIKAYCE liposomal is already approved or undergoing approval by national regulatory agencies following EMA approval. The literature review focused on the possibly variable spectrum of the "limited treatment options" definition in MAC-PD patients without cystic fibrosis (CF). The panel experts could comment on the papers online to generate ideas and start a discussion on the topic.

- Preliminary activities also foresaw gathering an **online collection of real-life cases** personally faced by the panel experts during their clinical activities. The Scientific Director developed the real-life cases into several draft iconic examples of possibly "limited treatment options" in managing MAC-PD patients without identifying the case authors. However, although deriving from real clinical situations, such draft iconic examples cannot claim to be exhaustive of the original clinical cases. Even if overall similar to the represented iconic problem, patients are always different — for instance, because of comorbidities and general health status — and individualized strategies might be warranted, possibly different from the suggested expert opinion. Before the Consensus Conference, the panel experts reviewed the iconic draft examples and blindly voted online to decide if they considered them realistic models of "limited treatment options" in MAC-PD management. The experts had the following assessment options: "Yes, an example of limited treatment option"; "No, not an example of limited treatment option"; "Not enough information to decide".

  During the Milan Consensus Conference, the panel experts:
  - Reviewed and extensively discussed the typical examples and the preliminary evaluations attributed to them.
  - Modified the typical example descriptors (from now on, "statements") to reach a consensus about their relevance as realistic clinical possibilities.

  As a final step, the panel members voted according to the Delphi method on each iconic example/statement to confirm if, according to their expert opinion and experience (attributed scores variable from 0 or "completely irrelevant" to 10 or "totally relevant"):

- Each iconic example/statement does or does not qualify as an actual MAC-PD "limited treatment option".
- ARIKAYCE liposomal might have a role in the real-life management of such situations.

The Consensus Conference in Milan

Table 1 lists the fourteen experts invited to the MACPaLTO Consensus Conference who effectively attended the meeting. Only twelve experts participated in the Delphi voting procedures on February 22nd—Prof. Shteinberg attended only on the second day; Prof. Alberti, as chairman of the Organising Committee and the Consensus Conference, did not vote on February 22nd but participated in voting procedures only on the second day. Four European experts, although invited, could not attend the Consensus Conference (Table 2). However, they variably participated in the activities described in the "Preliminary activities in preparation for the Consensus Conference in Milan" section.

After self-presentations on the first conference day (February 22nd), the very first discussion focused on the real meaning of "limited treatment option" (from now on, LTO) and trying to dispel at least some ambiguities in the EMA definition that may arise during actual clinical activities. Other diseases and situations, like multiple myeloma after third-line treatment or HIV treatment failure after exposure to different classes of drugs, were not deemed to help cast light on the problem and were therefore not included in the case examples.

- The expert panel agreed that the EMA definition of actual LTO boundaries does appear undefined—either too extensive or limited. For instance, might an LTO situation arise when therapy deviates from rigorous first-line GBT indications, as when clofazimine might be needed to replace one of the first-line antimicrobials? In vitro and mice models suggest the effectiveness of clofazimine in MAC-PD, as does experience in patients with MAC-PD (retrospective data DOI: 10.1378/chest.15-0543) and tuberculosis. On the other hand, some local guidelines and practices imply a five-drug first-line treatment by adding amikacin and clofazimine to the standard three-antimicrobials GBT regimen in selected (severe) cases. Some experts also observed that the definition of the GBT regimen might leave some doubt because diet, respiratory physiotherapy, and surgery also have a role in MAC-PD management. Guidelines should define that role more clearly within the three-drug GBT framework. Other experts remarked that the GBT success rate not exceeding 60% after two years confirms the blurred LTO boundaries, possibly needing two more extensive and more limited definitions.

- The first decision by the panel of experts and thought leaders in pneumology focused on trying to reconcile the EMA and FDA differences in their respective "Therapeutic Indications". Attention initially centred on the descriptor "refractory". Although the term has no place in the EMA statement, the experts discussed if the EMA definition of

"refractory" disease was to be considered a "limited treatment option" in MAC-PD patients.

- Provided that macrolide sensitivity is verified and the patient may yield a suitable sputum sample, the panel agreed that **evidence-based support exists to consider all patients with refractory MAC-PD (**according to the 2020 ATS/ERS/ESCMID/IDSA clinical practice guideline**) as a "limited treatment option"**.

- All fourteen experts agreed that ARIKAYCE liposomal has a role in those LTO patients. However, opinions were not homogeneous regarding the optimal timing of starting ARIKAYCE liposomal. All experts agreed on starting ARIKAYCE liposomal for refractory MAC-PD patients with smear-negative nodular bronchiectatic disease, while twelve experts (85.7%) agreed to start ARIKAYCE liposomal for refractory MAC-PD diagnosis also in smear-positive nodular bronchiectatic disease. Two experts suggested starting intravenous amikacin in refractory MAC-PD diagnosis with smear-positive nodular bronchiectatic disease and then shifting to ARIKAYCE liposomal at a later stage.

- Nine experts (64%) would administer ARIKAYCE liposomal at diagnosis of refractory MAC-PD in newly cavitary disease independently of smear results. One dissenting expert suggested a sequential approach, with ARIKAYCE liposomal only after intravenous amikacin; others disagreed with variable preferences because of the lack of solid evidence about the relative efficacy of ARIKAYCE liposomal and intravenous amikacin. Conversely, others disagreed with varying opinions because there is no concrete evidence about the comparative effectiveness of ARIKAYCE liposomal and intravenous amikacin in these patients. Table 3 summarises the expert outcomes about considering patients with refractory MAC-PD as limited treatment options".

- **Beyond this first topic, "refractory MAC-PD as LTO", the two-day discussion focused on seven iconic examples/statements of <u>possible</u> "limited treatment options"**. Because of the lack of solid literature pieces of evidence for such examples/statements (in Table 4 from the second to the last one), they currently qualify as no more than **clinically reasonable expert opinions based on experience**. Table 4 summarises the MAC PaLTO overall conclusions.

- The iconic example proposed at this discussion stage is that of a MAC-PD due to **macrolide-resistant with/without amikacin-resistant strain**. All experts agreed that MAC-PD due to a macrolide-resistant strain translates into an LTO situation independently of the nodular bronchiectatic or cavitary radiological phenotype. All experts also agreed

that MAC-PD due to a macrolide-resistant strain translates into an LTO situation independently of the sensibility/resistance to amikacin (see Table 4.a). All the experts also agreed that ARIKAYCE liposomal should be considered as part of the treatment in all these LTO situations; however, in the case of both macrolide and amikacin-resistant MAC strains, only half of the experts suggested using ARIKAYCE liposomal. Regarding the timing of ARIKAYCE liposomal administration, the experts considered it doubtful since there is no prospective evidence to guide the decision. Table 4.a summarises the outcomes of expert discussions.

- The discussed iconic examples then focused on forced macrolide, ethambutol, or rifampin/rifamycins discontinuation for any reason—e.g., gastrointestinal intolerance or QTc prolongation, optic neuropathy and chiasmopathy for ethambutol, allergy for rifamycins (rifabutin and, to a lesser degree, rifampicin).
  All fourteen experts agreed that a macrolide or ethambutol discontinuation should be considered an LTO situation. Most panel experts (78.6%) refused the LTO definition in case of forced discontinuation of rifampin, considering the addition of clofazimine or a two-drug regimen (ethambutol and a macrolide) as an alternative option. Macrolide intolerance is of utmost importance. No effort should be spared to preserve the macrolide cornerstone in MAC-PD management—for instance, by switching between different macrolides or trying a desensitization protocol. Some experts would consider intravenous amikacin as an alternative worth an attempt. All the experts agreed on using ARIKAYCE liposomal as part of the treatment of MAC-PD patients in case of inability/discontinuation to take macrolides for whatever reason. This decision would not be the case in MAC-PD patients in case of inability/discontinuation to take ethambutol for whatever reason; in this situation, other options (such as clofazimine) should be considered. Table 4.b summarises the outcomes of expert discussions on forced macrolide, ethambutol, and rifampin/rifabutin discontinuation for any reason.

- The expert panel considered the inability to administer intravenous amikacin when advocated by MAC-PD guidelines or the premature discontinuation of intravenous amikacin (i.e., less than three months' treatment duration) as LTO situations. The whole board would resort to ARIKAYCE liposomal, provided there is no contraindication to inhaled amikacin, in all patients where intravenous amikacin is not or is no longer an option (Table 4.b).

The guideline definition of "refractory" MAC-PD is rigidly microbiological. However, the panel recognizes the possibility of being unable to collect microbiological samples during

treatment. Expert opinions were also variable about the indication to perform a bronchoscopy after six months of treatment. Most experts thought it preferable to have a CT scan after six months and carry out a bronchoscopy only after twelve months. The panel agreed that if there is no long-term clinical and radiological improvement, other causes, such as chronic infection with *Pseudomonas aeruginosa* or *Aspergillus*, should be excluded, reinforcing the case for looking into other infectious causes whenever possible. The expert panel agreed with the need for microbiological data to define a refractory MAC-PD as LTO.

- All experts agreed in considering a relapse (according to the NTM-net definition paper) in patients who underwent GBT (and assuming that it is not a reinfection) as LTO, Table 4.c. In this case, all the experts agreed to use ARIKAYCE liposomal as part of the treatment.

The meeting ended with the commitment to summarise the outcomes in a Consensus Document that the MAC-PaLTO Consensus Conference members will publish in the future. Hopefully, the future Consensus Document will help to dissipate some of the ambiguities faced by pneumologists and unsolved under the current LTO definition by EMA.

TABLES

Table 1. The experts who attended the MAC-PaLTO Consensus Conference.

N	Title	Surname	Name	Nationality	Affiliation
1	Prof.	Aliberti	Stefano	Italy	Professor, Humanitas University, Milan, Italy
2	Prof.	Blasi	Francesco	Italy	Professor, Pathophysiology and Transplantation, University of Milan, Italy
3	Prof.	Burgel	Pierre-Régis	France	Professor of Respiratory Medicine, Université Paris Cité, Inserm U1016, Institut Cochin and Assistance Publique Hôpitaux de Paris, France
4	Ass. Prof.	Calcagno	Andrea	Italy	Associate Professor, Department of Medical Sciences, Infectious Diseases, University of Turin, Italy
5	Dr	Grogono	Dorothy	United Kingdom	Respiratory Consultant, Thoracic, Royal Papworth Hospital, United Kingdom
6	Prof.	Loebinger	Michael	United Kingdom	Consultant pulmonologist, Host Defence Unit, Royal Brompton Hospital, London, United Kingdom
7	Dr	Papavasileiou	Apostolos	Greece	"Sotiria" Thoracic Diseases General Hospital of Athens, Greece
8	Dr	Polverino	Eva	Spain	Pulmonologist, Respiratory Medicine, Adult Bronchiectasis and Cystic Fibrosis, University Hospital Vall D'Hebron, Barcelona, Spain
9	Prof.	Rohde	Gernot	Germany	Physician, Respiratory Medicine, University Hospital Frankfurt, Germany
10	Dr	Salzer	Helmult	Austria	Physician, Department of Internal Medicine 4 - Pneumology, Kepler University Hospital, Austria
11	Prof.	Shteinberg	Michal	Israel	Carmel Medical Center and the Technion- Israel Institute of Technology, Faculty of Medicine, Haifa, Israel
12	Prof.	Van Braeckel	Eva	Belgium	Pulmonologist - Infectious Disease physician, Department of Respiratory Medicine, Ghent University Hospital, Belgium; Assistant Professor, Department of Internal Medicine and Paediatrics, Ghent University, Belgium
13	Prof.	Veziris	Nicolas	France	Bacteriologist, Sorbonne Université, APHP, NRC for Mycobacteria, Paris, France
14	Prof.	Wagner	Dirk	Germany	Department of Internal Medicine II, Division of Infectious Diseases, Medical Center, University of Freiburg, Germany

Table 2. The European experts who, although invited and actively participating in preparatory activities, could not attend the MAC-PaLTO Consensus Conference.

N	Title	Surname	Name	Nationality	Affiliation
	Dr	Floe	Andreas	Denmark	Department of Respiratory Diseases, Aarhus University Hospital, Denmark
	Dr	Prados	Concepción	Spain	Pulmonology, cystic fibrosis, bronchiectasis, bronchial infections, La Paz University Hospital, Spain
	Dr	Sánchez-Montalvá	Adrián	Spain	*International Health Unit Vall d'Hebron-Drassanes. Infectious Diseases Department. Vall d'Hebron University Hospital. Barcelona, Spain *National Referral Centre for Tropical Diseases (CSUR) *Center for Biomedical Research in Infectious Diseases Network (CIBERINFEC), Institute of Health Carlos III, Madrid, Spain.
	Dr	van Ingen	Jakko	The Netherlands	Consultant Clinical Microbiologist, Medical Microbiology, Radboud University Medical Center, The Netherlands

Table 3. Considering patients with refractory MAC-PD at "limited treatment option" and the role of ARIKAYCE liposomal.

Situation	Is this a. LTO situation?		Would you use ARIKAYCE liposomal as part of your treatment?		Would you use ARIKAYCE liposomal from the beginning?		Notes
	YES	NO	YES	No	YES	NO	
Refractory MAC-PD — smear-negative nodular-bronchiectatic disease	14 (100%)	0	14 (100%)	0	14 (100%)	0	
Refractory MAC-PD — smear-positive nodular-bronchiectatic disease	14 (100%)	0	14 (100%)	0	12 (86%)	2 (14%)	Two experts would start with IV amikacin with a later (possibly) shift to ARIKAYCE liposomal.

Refractory MAC-PD — new cavitary irrespective of smear outcomes	14 (100%)	0	14 (100%)	0	9 (64%)	5 (36%)	One expert: sequential approach starting with IV amikacin; four experts: variable or undefined opinions (due to lack of evidence supporting IV vs. Arikayce).

Table 4. Examples of possible "limited treatment options" according to clinical experience and expert opinion at the MAC-PaLTO Consensus Conference panel and suggested role of ARIKAYCE liposomal.

	Situation	**Is this an LTO situation?**		**Would you use ARIKAYCE liposomal as part of your treatment?**		**Notes**
		YES	**NO**	**YES**	**No**	
a. Macrolide-resistant strain	Newly diagnosed, non-cavitary, MAC-PD due to a macrolide-resistant, amikacin-sensitive **(≤64 μg/ml)** strain	14 (100%)	0	14 (100%)	0	No direct evidence exists about the ideal timing for starting administration; moreover, there might be administrative problems with repayment.
	Newly diagnosed, cavitary, MAC-PD due to macrolide-resistant, amikacin-sensitive **(≤64 μg/ml)** strain	14 (100%)	0	14 (100%)	0	No direct evidence exists about the ideal timing for starting administration; moreover, there might be administrative problems with repayment.
	Newly diagnosed MAC-PD due to a macrolide-resistant, amikacin-intermediate strain	14 (100%)	0	14 (100%)	0	No direct evidence exists about the ideal timing for starting administration; moreover, there might be administrative problems with repayment.
	Newly diagnosed MAC-PD due to a macrolide-resistant, amikacin-resistant **(>64 μg/ml) strain**	14 (100%)	0	7 (50%)	7 (50%)	Half of the group would not give ALIS because of resistance, but the other half will use it due to the lack of other options. After testing amikacin sensitivity, outcomes could be different with inhaled amikacin. Testing for sensitivity to inhaled amikacin would be ideal.
b. Inability to take drugs	**Inability to take macrolides for whatever reason**	14 (100%)	0	14 (100%)	0	All efforts should be attempted to keep the macrolide switching within the class. Premature discontinuation should be considered. Some experts will start with Amikacin IV according to patient preferences or needs.

	Inability to take ethambutol for whatever reason (e.g., allergy, adverse events, …)	14 (100%)	0	3 (21%)	11 (79%)	Consideration should be on oral drugs and other suitable options (e.g., clofazimine).
	Inability to use rifamycins for whatever reason	3 (21%)	11 (79%)	0	14 (100%)*	Consider switching within the class or maintaining a two-drug regimen if one of the two drugs is a macrolide and the strain is macrolide sensitive. Clofazimine could be considered. *The three experts, considering that as an LTO situation, also voted "no.
	Inability to use/tolerate intravenous amikacin when indicated (e.g., smear positive, cavitary disease) for any reason.	14 (100%)	0	14 (100%)	0	If no contraindications exist.
c. Relapse	**Relapse, according to NTM-net definition, in a patient who underwent guideline-based therapy, assuming it is not a reinfection.**	14 (100%)	0	14 (100%)	0	DST is crucial and should be considered while deciding about treatment. All efforts should be made to distinguish reinfection from relapse: e.g., education of laboratories to store primary isolates to be able to compare secondary isolates by whole genome sequencing and prove reinfection once the isolates differ from each other. If considered a relapse, this situation is equivalent to refractory. The frequency of microbiology work-up is essential. Compliance with treatment should be considered.
d. Reinfection	**Reinfection according to NTM-net definition after stopping treatment**	0	14 (100%)	0	14 (100%)	