



# Inhalation: The Inspired Choice in the Treatment of Respiratory Disease

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## Introduction

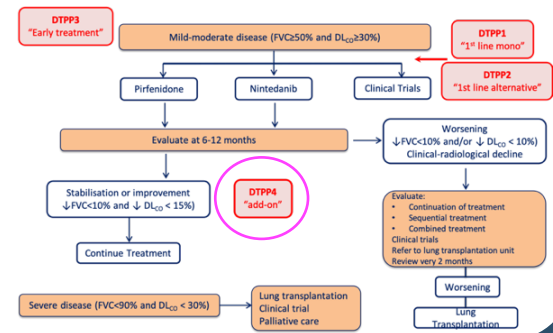
- We have recently been reflecting on the projects that we have supported since founding TherapeutAix 3 years ago
- Twenty projects were in the respiratory space, with the following breakdown
  - IPF – 16 projects
  - Inhaled – 9 projects (5 of which have been in the last year)
  - COPD – 3 projects
  - Other – 1 project
- Based on our experience, and our understanding of the benefits of inhaled delivery in respiratory disease (“to the lung for the lung”), we find it puzzling that inhalation is not being pursued to a greater extent in new approaches to the treatment of Idiopathic Pulmonary Fibrosis (IPF) and in the prevention / treatment of COVID-19

## The missed opportunity?

- Inhaled bronchodilators and steroids, used singly or in combination, are the mainstay of pharmacological management of asthma and COPD
- This validates direct delivery to the airway leading to effective airway and lung tissue concentrations and reduced systemic exposure and side effects (SEs)
- For many of the approaches being considered for IPF and COVID-19, the potential for systemic SEs may be prohibitive
- Therefore – with the asthma / COPD precedent –, why isn't inhalation being considered as a preferred delivery option in IPF and COVID-19?

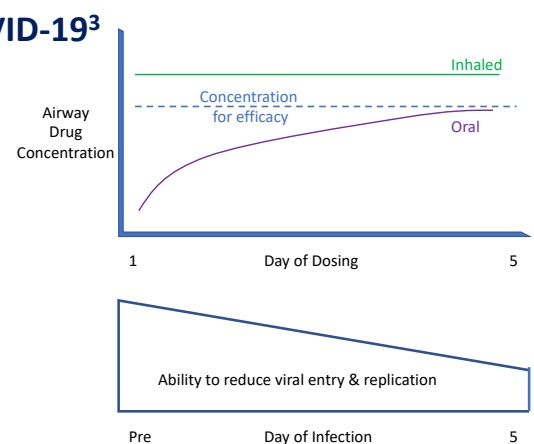
## Inhaled delivery in IPF; perception & reality

- There is a perception that inhaled drug delivery could be compromised in IPF patients. However, lung distribution studies with salbutamol (as a marker compound) showed that it is possible to achieve and optimise drug delivery to the peripheral airway in IPF patients<sup>1</sup>
- New approaches to treat IPF will need to be compatible with the current standard of care<sup>2</sup> as **add-on therapy** (at least initially). Given the significant SEs with both oral pirfenidone and nintedanib, add-on of new mechanisms in systemic therapy is highly likely to lead to additive SEs and/or DDIs. Inhalation, by virtue of reduced GI and systemic exposure, may represent the only means to enable the potential for a number of new approaches



## Inhaled Delivery in Prevention/Early Treatment of COVID-19<sup>3</sup>

- Prevention or early treatment of SARS-CoV-2 infections would ideally target the “point of entry” or the “point of damage” of the virus, the respiratory tract and airway epithelium. Treatment needs to be rapid and aggressive to inhibit or prevent viral entry, replication, and local or systemic inflammatory responses
- Antiviral drug concentrations at the site of action (the airway epithelium) are more relevant than plasma concentrations for efficacy, and the targeted concentrations should be based on the EC<sub>90/95</sub> for inhibition of viral replication
- With oral delivery, airway exposure and effect is dependent on systemic PK – multiple doses (days) may be required to achieve effective concentrations
- With inhaled delivery, airway exposure and efficacy is achieved with a lower total dose, lower systemic exposure and reduced systemic SEs – and relevant exposure is achieved instantaneously leading to immediate onset of effect



## Some Considerations

- Optimising molecules for inhaled delivery is not straightforward
- Should be considered in an integrated manner early in a discovery project, rather than as an afterthought
- Direct lung delivery can reduce systemic SEs, but can also bring a new set of SEs that need to be factored-in to the overall efficacy/safety/adherence assessment
- While upper airway irritancy is a potential complication of inhaled delivery, not all device and formulation options are the same and there is a high likelihood of detecting, understanding, and de-risking this early in the clinical programme

## Conclusions

- Inhaled delivery can enable new pharmacological approaches in respiratory disease that may otherwise not be realised
- The perceived blockers include
  - Perceptions of difficulty
  - Nervousness / limited experience
  - Lack of awareness?
- To enable more successful drug developments for respiratory diseases, inhaled administration should be evaluated early in R&D projects

## References

- <sup>1</sup>Usmani et al, The topical study of inhaled drug (salbutamol) delivery in idiopathic pulmonary fibrosis. Respiratory Research (2018) 19:25 ([https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5801831/pdf/12931\\_2018\\_Article\\_732.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5801831/pdf/12931_2018_Article_732.pdf))
- <sup>2</sup>Cruwys et al, Drug discovery and development in idiopathic pulmonary fibrosis: challenges and opportunities. Drug Discovery Today (2020) 25(12), 2277-2283 (<https://doi.org/10.1016/j.drudis.2020.09.019>)
- <sup>3</sup>Humphries et al, 'Inhalation therapies for COVID-19', Faculty of Pharmaceutical Medicine blog, 28 January 2021 (<https://www.fpm.org.uk/blog/inhalation-therapies-for-covid-19/>)