ILD highlights from the ERS 2023 Congress

(Tiêu điểm về bệnh phổi mô kẽ tại Hội nghị Hô hấp Châu Âu 2023)

Milan, 09 – 13 tháng 09, 2023

Boehringer Ingelheim

External report, SC-CRP-14278, NP-VN-100020

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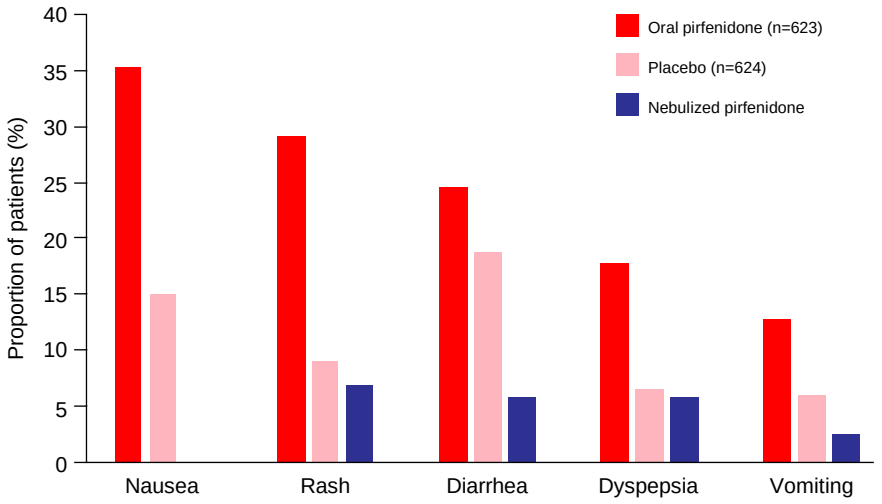
Boehringer Ingelheim

Nebulized pirfenidone in IPF: first look at FVC data[1] (West A *et al.*)

(Pirfenidone hít trong IPF : quan sát ban đầu từ dữ liệu FVC)

- The Phase Ib ATLAS trial investigated the safety, tolerability and efficacy of inhaled pirfenidone (AP01) in patients with IPF[2]
- A **Phase II, open-label extension** of the ATLAS trial is ongoing and aims to assess the safety and efficacy of nebulized pirfenidone in patients with IPF or PPF (ACTRN12621000170820; **N=100**)[3]
  - 72 patients with IPF were recruited; 41 patients participated in the Phase Ib study (cohort 1), while 31 patients were newly enrolled (cohort 2); FVC data were available for 48 patients with IPF at 48 weeks
  - The trial was also open to patients with PPF (n=28); first look data for these patients were reported separately[4]
- The mean (SD) change in FVC from baseline at 48 weeks was −165.5 (±242.6) mL and −151.1 (±358.9) mL for cohorts 1 and 2, respectively
  - Previously published clinical trial data comparing oral pirfenidone with placebo in IPF demonstrated a mean change in FVC from baseline to 52 weeks of −235 mL and −428 mL for oral pirfenidone and placebo, respectively[5]
- Nebulized pirfenidone was well-tolerated, with gastrointestinal AEs markedly reduced compared with previously published clinical trial data of oral pirfenidone in IPF (**Figure**)[6]

Figure. Incidence of selected AEs in patients with IPF treated with placebo, oral pirfenidone or nebulized pirfenidone



Author conclusion: This first look at the FVC data, and the improved side effect profile compared with oral pirfenidone, suggests that nebulized pirfenidone is a promising development for the treatment of patients with IPF, and warrants further investigation.

1. West A *et al.* Oral presentation at ERS International Congress 2023:OA2582; 2. West A *et al Thorax* 2023;78:882–9; 3. ACTRN12621000170820. Available at: https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ID=380951 (accessed September 2023); 4. West A *et al.* Poster presentation at ERS International Congress 2023: PA405; 5. King Jr TE *et al. N Engl J Med* 2014;370:2083–92; 6. Noble PW *et al. Eur Respir J* 2016;47:243–53

Safety, tolerability and antifibrotic activity of bexotegrast: Phase IIa INTEGRIS-IPF study (NCT04396756)[1] (Wuyts WA *et al.*; Sponsor: Pliant Therapeutics)

(Độ an toàn, tính dung nạp và tính kháng xơ của Bexotegrast : Nghiên cứu pha IIa INTEGRIS-IPF)

- Bexotegrast is an oral, dual-selective inhibitor of $\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrins
- This **multicenter, randomized, placebo-controlled, Phase II trial** assessed the safety and tolerability of bexotegrast, and the durability of its effects on FVC and QLF in patients with IPF
  - Patients were randomized to receive once-daily treatment of 40 mg, 80 mg, 160 mg, or 320 mg of bexotegrast or placebo for 12 weeks
  - Only patients in the bexotegrast 320 mg (**n=21**) and placebo (**n=8**) groups continued treatment for at least 24 weeks (efficacy) and up to 48 weeks (safety)*
  - Data from the 12-week analysis, incorporating all treatment arms, have previously been reported[2]
- At baseline, 81.8% and 75.0% of patients were receiving background antifibrotics in the bexotegrast 320 mg and placebo groups, respectively
- At Week 24 (exploratory efficacy endpoint), bexotegrast reduced FVC decline by 67% relative to placebo (**Figure A**; *P*>0.05); bexotegrast in addition to a background antifibrotic reduced FVC decline by 80% relative to background therapy alone (**Figure B**; *P*>0.05)
- A numerically smaller increase in mean QLF score was seen from baseline to Week 12, and from baseline to Week 24, in patients treated with bexotegrast vs placebo
- Over 40 weeks of treatment, AEs were reported by 90.9% and 87.5% of patients in the bexotegrast and placebo groups, respectively
  - Most AEs were mild or moderate in severity and no drug-related SAEs were reported
  - There were no discontinuations due to AEs from Week 12 to Week 40

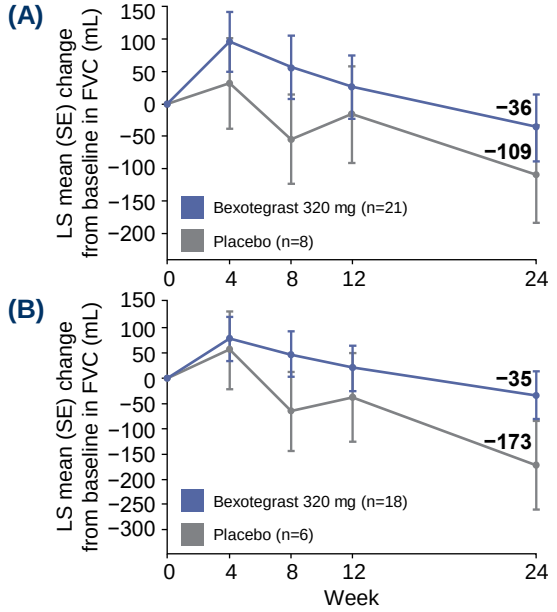


Figure. Change in FVC from baseline to Week 24 in patients with IPF in the full ITT population (**A**) and patients in the ITT population who were receiving background antifibrotic therapy (**B**)

Author conclusion: Bexotegrast 320 mg was well tolerated in participants with IPF for up to 40 weeks of treatment. There was evidence of a durable treatment effect on FVC over 24 weeks. QLF evaluation supports the antifibrotic mechanism of bexotegrast. The current study was designed to assess safety and tolerability and was not powered to adequately assess efficacy with relatively small patient populations and limited treatment duration. Late-stage evaluation of bexotegrast was initiated in mid-2023 in the BEACON-IPF study.

*The longest duration of evaluation was at Week 40

1. Wuyts WA *et al.* Oral presentation at ERS International Congress 2023: OA1423; 2. Lancaster LH *et al. Am J Respir Care Med* 2023;207: A2777

Abbreviations are defined in the slide notes

Efficacy and safety of danazol for pulmonary fibrosis associated with telomere related gene mutation[1] (Sicre De Fontbrune F *et al*.)

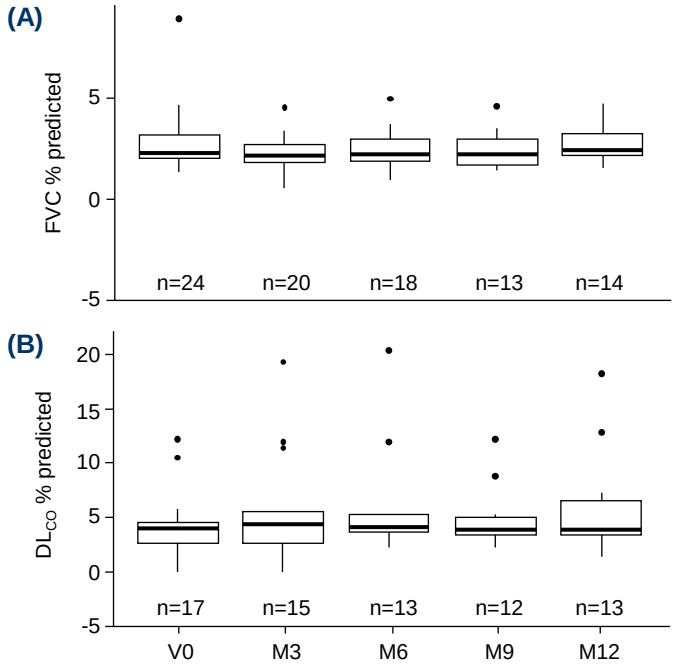
(Hiệu quả và độ an toàn của Danazol trong xơ phổi kèm telomere liên quan đột biến gen)

IPF

- Cases of pulmonary fibrosis that are related to mutations in telomere-related genes (TRGs) are severe (mean FVC decline: 300 mL/year)[2]
- Danazol is a synthetic androgen that may activate telomerase, increase telomere length, and improve hematological disease[3]
- This **multicenter, open-label Phase II trial** (ANDROTELO; NCT03710356) included patients (**N=25**) with a pathogenic or likely pathogenic TRG variant, and pulmonary fibrosis (>10% on CT scan) or hematologic involvement*
  - Patients received danazol 400 mg bid for 12 months
- At baseline, median age was 57.5 years, median FVC % predicted was 69% and median DL_{CO} % predicted was 44%
- Only 10 of 25 patients completed 12 months of danazol treatment
  - The remaining 15 patients discontinued due to side effects (n=9), death (n=3), lung transplant (n=1), pulmonary fibrosis progression (n=1), or withdrawal of consent (n=1)
- Fourteen patients were evaluated for efficacy at Month 12 (**Figure**)
  - The relative decline in FVC % predicted was 2% (CI: 1.7–15.6) and the relative decline in DL_{CO} % predicted was 7.4% (CI: 0.5–13.0)
  - No significant differences in telomere length were observed from baseline to Month 12 (*P*=0.14)

Author conclusion: While danazol might be a therapeutic option for hematological disease related to TRG mutations, the ANDROTELO study showed poor tolerance of danazol in patients with pulmonary fibrosis and TRG mutations. AEs of danazol make its long-term use unlikely for pulmonary fibrosis. New targeted therapeutic options will have to be developed, including considerations for relatives.

Figure. Relative decline in FVC % predicted (**A**) and DL_{CO} % predicted (**B**) over 12 months in patients with a pathogenic or likely pathogenic TRG variant, and pulmonary fibrosis or hematologic involvement



*Platelets <20 g/L, neutrophils <0.5 g/L, hemoglobin <8 g/dL or transfusion

1. Sicre De Fontbrune F *et al.* (presented by Borie R) Oral presentation at ERS International Congress 2023: OA2580; 2. Newton CA *et al. Eur Respir J* 2016;48:1710–20; 3. Townsley DM *et al. N Engl J Med* 2016;374:1922–31

Effect of BI 1015550, a preferential PDE4B inhibitor, on gene expression profiles and lung function in IPF[1] (Richeldi L *et al.*; Sponsor: Boehringer Ingelheim)

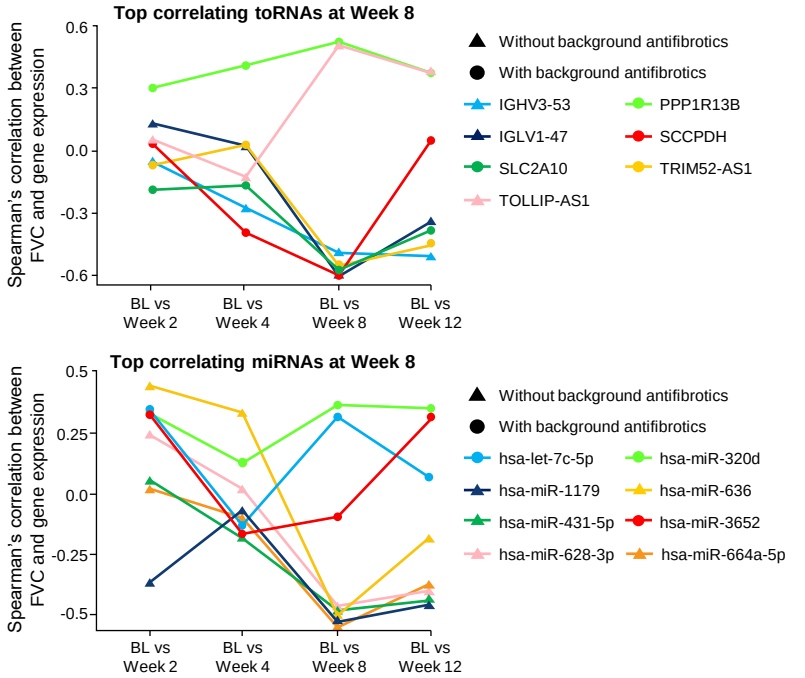
IPF

(Hiệu quả của BI 1015550, một chất ức chế PDE4B ưa thích, trên hồ sơ biểu hiện gene và chứ năng phổi trong xơ phổi vô căn – IPF)

- In a Phase II trial, BI 1015550 prevented FVC decline over 12 weeks in patients with IPF[2]
  - *Post-hoc* analyses revealed that BI 1015550 reduced markers of inflammation, epithelial injury and fibrosis[3]
- In this **gene expression analysis**, blood samples obtained during the Phase II trial were used to investigate whether treatment with BI 1015550 bid and/or changes in FVC are associated with up- or downregulation of specific genes and miRNAs (**N=147**)
  - ToRNA and miRNA were isolated from peripheral blood cells and plasma of patients treated with BI 1015550 bid, respectively
  - Gene expression was analyzed by differentially expressed gene (DEG) analysis and Ingenuity Pathway Analysis (IPA[4]), and was correlated with changes in FVC and use of background antifibrotics
- BI 1015550 had a weak but significant effect on the expression of genes that have been linked to fibrosis and IPF when compared with baseline (P<0.01; data not shown)
- There was a significant correlation between change from baseline in the expression of fibrosis-linked genes, and change in FVC (**Figure**)
  - This correlation was observed in patients irrespective of background antifibrotic use

Author conclusion: BI 1015550 prevented a decline in lung function over 12 weeks in patients with IPF,[2] with a reduction in protein biomarkers of fibrosis and inflammation in peripheral blood.[3] Differentially expressed gene analysis showed limited effects of BI 1015550 on gene expression. Small but significant changes in gene expression, in genes associated with inflammation and fibrosis by IPA, correlated with changes from baseline in FVC. Changes/correlations were seen in patients with or without background antifibrotic treatment.

Figure. Spearman's rank correlation between % change from baseline in FVC and fold change from baseline in gene expression in patients with IPF treated with BI 1015550 bid*



*Gene expression was ranked based on the strength of the correlation between fold change with the change in FVC at Week 8 (all P<0.05); the most highly correlated genes with a previously reported link to fibrosis are shown

1. Richeldi L *et al.* Oral presentation at ERS International Congress 2023: OA2584; 2. Richeldi L *et al. N Engl J Med* 2022;386:2178–87; 3. Maher TM *et al.* Poster presented at the International Colloquium on Lung and Airway Fibrosis 2022; 4. QIAGEN Inc. Ingenuity Pathway Analysis. Available at: https://www.qiagen.com/us (accessed September 2023)

Abbreviations are defined in the slide notes

Nasal stimulation with L-menthol alleviates multidimensional breathlessness in patients with ILD: a randomized controlled trial[1] (Kanezaki M *et al.*)

(Kích thích mũi bằng L-menthol giảm khó thở đa hướng trên bệnh nhân ILD – một thử nghiệm RCT)

- This **randomized, placebo-controlled, cross-over study** (MeDILD) evaluated the efficacy of olfactory stimulation with L-menthol in alleviating breathlessness in patients with stable fibrotic ILD (jRCT1030220389; **N=43**)
  - L-menthol (along with a TRPM8 agonist) and placebo were administered through patches placed on the inside of a face mask; the sham condition was breathing through a facemask without a patch
  - After a baseline challenge of breathing for 2 minutes without inspiratory resistance loading, patients were randomized to breathe for 2 minutes with inspiratory resistance loading under either the L-menthol, placebo or sham condition;* patients then switched intervention following a 20-minute rest period[2]
  - Sensory and affective dimensions of breathlessness were evaluated using the Japanese MDP†[3]
- For the sensory dimension, L-menthol significantly reduced breathing discomfort and air hunger when compared with placebo or sham, and mental and physical breathing effort when compared to placebo (**Figure**); however, no significant differences were observed for chest tightness or hyperpnea
  - The mean differences between L-menthol and placebo in breathing discomfort, air hunger, mental breathing effort and physical breath effort were −2.58, −1.67, −1.44 and −1.23, respectively
  - L-menthol did not significantly affect any component of the affective dimension when compared with placebo or sham
- During inspiratory resistive loading, L-menthol also significantly increased the cognition of inspiratory flow (CIF) vs sham and placebo, although no significant changes in the mean inspiratory flow rate were observed between conditions
- No significant differences in breathing pattern, inspiratory or expiratory time, breathing frequency or inspiratory neural drive were observed between L-menthol, placebo and sham

Figure. Comparisons of breathing discomfort (**A**), air hunger (**B**), physical breathing effort (**C**) and mental breathing effort (**D**) during inspiratory resistive loaded breathing under L-menthol, placebo and sham conditions. **P*<0.005

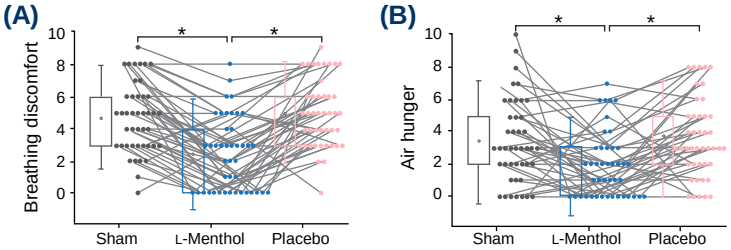


Figure from Kanezaki M *et al. Eur Respir J* 2023; doi: 10.1183/13993003.02453-2022.
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Author conclusion: L-menthol acts as a selective agonist in the airway TRPM8 channels and induces a cooling sensation in the airway without altering the inspiratory neural drive and pattern. Augmented TRPM8 afferent inputs via L-menthol inhalation may lead to the dissociation between the mean inspiratory flow rate and CIF during L-menthol stimulation. This may improve the dissociation between the ventilatory descending output and the incoming afferent ventilator information from the peripheral sensory nerves.

*The imposed resistance was 20 and 30 $cmH_2O \cdot L^{-1} \cdot s^{-1}$ in patients with predetermined P_{Imax} <60 cmH_2O and ⩾60 cmH_2O, respectively; †The sensory dimension measures the intensity of five sensory qualities (physical and mental breathing effort, air hunger, tightness and hyperpnea) and the affective dimension measures the intensity of five emotions (depression, anxiety, anger, frustration and fear)

1. Kanezaki M *et al.* Oral presentation at ERS International Congress 2023: OA3258; 2. Kanezaki M *et al. Eur Respir J* 2023; doi:10.1183/13993003.02453-2022; 3. Banzett R *et al. Eur Respir J* 2015;45:1681–91

Abbreviations are defined in the slide notes