# Anti-Fibrotic and Mortality Reduction Potential of a Novel Long-Acting Glucagon/GIP/GLP-1 Triple Agonist (HM15211, Efocipegtrutide) in Preclinical Models of Idiopathic Pulmonary Fibrosis

**Jeong A Kim**, Wonki Kim, Seon Myeong Lee, Jong Suk Lee, Jung Kuk Kim, Sungmin Bae, Daejin Kim, Sang Hyun Lee, In Young Choi
Hanmi Pharm. Co., Ltd, Seoul, South Korea

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## ABSTRACT

HM15211 is a novel long-acting glucagon/GIP/GLP-1 triple agonist that has confirmed its anti-fibrotic efficacy in in vitro and in vivo liver fibrosis models and is currently undergoing phase 2 clinical trials. Based on its anti-fibrosis effect in the liver and its high distribution in the lungs, the efficacy in pulmonary fibrosis was evaluated as a new indication. Here, we evaluated the preclinical efficacy of HM15211 in bleomycin induced mouse model of IPF.

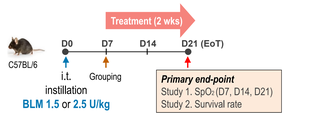
To investigate the therapeutic effect of HM15211 on pulmonary function, fibrosis as well as mortality, BLM induced mice models were established by either single intratracheal (i.t.) instillation or subcutaneous infusion. Also, to evaluate the efficacy of HM15211 on the subpleural region fibrosis like human IPF, 100 unit/kg BLM was subcutaneously infused for 7 days.

In 1.5 unit/kg BLM single instillation model, lung function was impaired at start of treatment and further exacerbated until the end of (84.0% at D7, 77.1% at D21, $SpO_2$). In contrast to the FDA-approved drugs for IPF (pirfenidone and nintedanib), HM15211 treatment significantly restored impaired lung function. In an additional IPF model with subcutaneous BLM infusion, the area of subpleural fibrosis was increased on day 14 after the start of BLM infusion, which worsened over the next 3 weeks. Similar to the anti-fibrotic efficacy in single BLM instilled model, HM15211 significantly decreased subpleural fibrosis area, total lung collagen, and Ashcroft score. Furthermore, decline in survival rate for 21 days in the 2.5 unit/kg BLM single instillation model (17%) was effectively inhibited by HM15211, nintedanib and pirfenidone. Notably, HM15211 showed improved survival rate (61%) compared to nintedanib (33%) and pirfenidone (28%), suggesting potential superiority of HM15211 over current IPF drugs.

HM15211 could possess therapeutic potential for IPF with improved treatment effects over current standard of care. Ongoing mechanistic studies will elucidate the underlying mode of actions, and human study should be followed up to assess the clinical relevance of these findings.

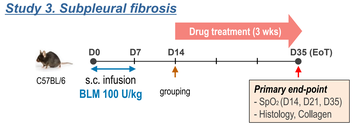
## METHODS

*Study 1. Pulmonary function / Study 2. Mortality rate*




- To evaluate therapeutic effect of HM15211 on impairment of pulmonary function during disease progression, a single dose of bleomycin (BLM) 1.5 U/kg [Study 1] or 2.5 U/kg [Study 2] was administered intratracheally.
- At days 7 after the BLM, HM15211 (or IPF drugs) was administered for 2 weeks. Pulse oximetry was measured on days 7 (baseline), 14 and 21 post BLM instillation [Study 1], and survival was monitored daily [Study 2].

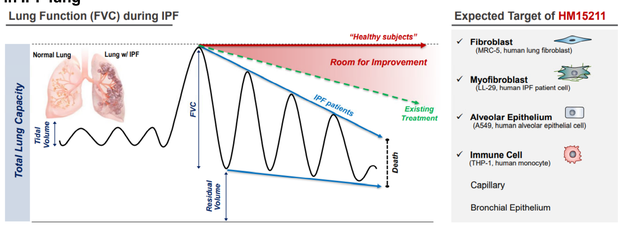
*Study 3. Subpleural fibrosis*




- To evaluate the efficacy of HM15211 on the subpleural fibrosis like human IPF, 100 unit/kg BLM was subcutaneously infused for 7 days.
- HM15211 was administered for 3 weeks from the 14th day after the BLM infusion initiation. Pulse oximetry was measured on days 14 (baseline), 21 and 35. The anti-fibrotic effect was evaluated by histopathology and collagen contents analysis.

## BACKGROUND

**Overview of alterations in lung function in IPF, and predicted anti-fibrotic and anti-inflammatory effects of HM15211 in IPF lung**







## RESULTS

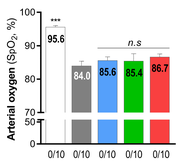
### Improvement of impaired pulmonary function in BLM mice

**Figure 1. Effect of HM15211 on pulmonary function in intratracheal BLM-induced model**

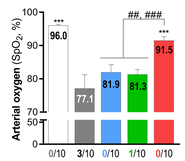
**(a) Changes in $SpO_2$** (D21-D7)


** ~ ***$p$ < 0.01 ~ < 0.001 *vs.* BLM, vehicle by One-way ANOVA
# ~ ###$p$ < 0.05 ~ < 0.001 vs. BLM, HM15211 by t-test

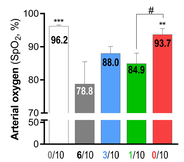
**(b) Arterial oxygen at D7** (Baseline)




**(c) Arterial oxygen at D14** (after 1w drug treatment)



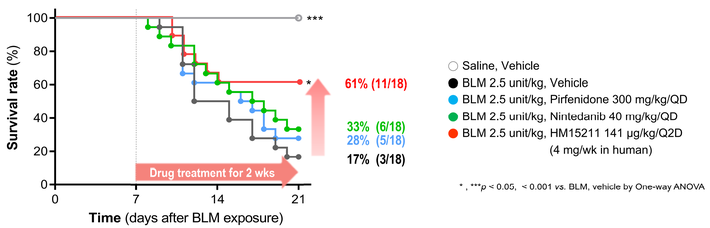

**(d) Arterial oxygen at D21** (after 2w drug treatment)




➢ Unlike the IPF drugs pirfenidone and nintedanib, the decrease in peripheral oxygen saturation ($SpO_2$) level by bleomycin was effectively restored by HM15211 at D21 to near normal level (93.7% *vs.* 96.2% for Saline vehicle).

### Improvement of survival rate in BLM mice

**Figure 2. Effect of HM15211 on mortality due to disease progression** (n=10~18)



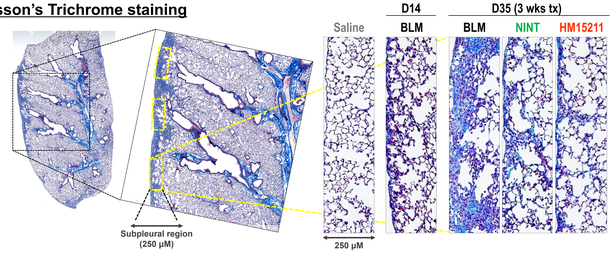

*, ***$p$ < 0.05, < 0.001 *vs.* BLM, vehicle by One-way ANOVA

➢ HM15211 significantly improved the survival rate of mice treated with 2.5 U/kg BLM from 17% to 61% unlike pirfenidone (28%) and nintedanib (33%), suggesting that HM15211 could slow disease progression and prolong survival in BLM-induced IPF mice

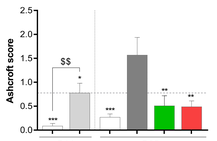
### Improvement of fibrosis and pulmonary function in subpleural fibrosis model

**Figure 3. Effect of HM15211 on progressive subpleural fibrosis**

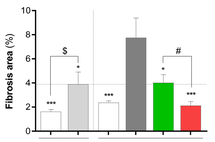
**(a) Masson's Trichrome staining**




**(b) Ashcroft score** (subpleural region)




**(c) Fibrosis area** (subpleural region)




**(d) Pro-collagen 1α1** (total)

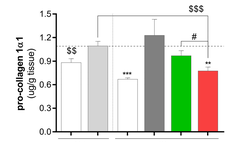
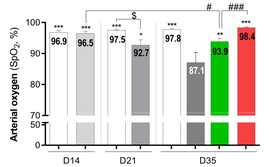
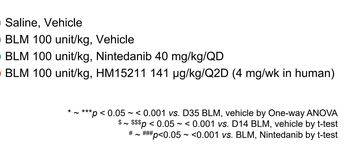



**Figure 4. Effect of HM15211 on pulmonary function in BLM infusion model**




* ~ ***$p$ < 0.05 ~ < 0.001 *vs.* D35 BLM, vehicle by One-way ANOVA
$ ~ $$$$p$ < 0.05 ~ < 0.001 *vs.* D14 BLM, vehicle by t-test
# ~ ###$p$<0.05 ~ <0.001 *vs.* BLM, Nintedanib by t-test

➢ Subcutaneous BLM infusion progressively increased subpleural fibrosis and decrease peripheral oxygen saturation ($SpO_2$). These detrimental effects were inhibited or reversed by HM15211 over 3 weeks of treatment, which was superior to nintedanib.

## CONCLUSIONS

- **HM15211, Glucagon/GIP/GLP-1 triple agonist, is designed to treat NASH and fibrosis by targeting multiple aspect of the disease (in Clinical phase 2).**
- **In intratracheal BLM instilled IPF model, HM15211 improved respiratory functional impairment and subsequently mortality.**
- **HM15211 also ameliorated sub-pleural fibrosis and respiratory function in subcutaneously infused BLM induced lung fibrosis mice.**
- **HM15211 has therapeutic potential for IPF with improved efficacy over the current standard of care in several nonclinical studies.**