Abstract #838

Anti-fibrotic potential of a novel long-acting Glucagon/GIP/GLP-1 triple agonist (HM15211) in preclinical models of idiopathic pulmonary fibrosis

Seon Myeong Lee, Jeong A Kim, Jong Suk Lee, Jung Kuk Kim, Young-Hwan Ban, Jong Soo Lee, Sung Min Bae, Dae Jin Kim, Sang Hyun Lee, In Young Choi

Hanmi Pharm. Co., Ltd., Seoul, Republic of Korea

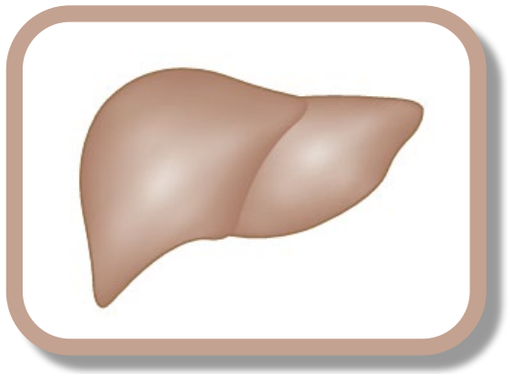
Hanmi

Presenter Disclosure

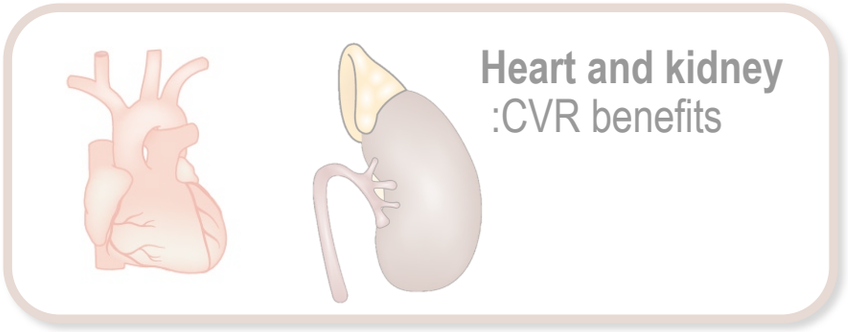
Employee of Hanmi Pharm. Co., Ltd.

Proposed indication expansion of HM15211

An excellent preclinical efficacy of HM15211 on liver fibrosis was confirmed (abstract #778)**. As HM15211 was distributed not only in the liver but also in the lung, potential benefits of HM15211 on pulmonary fibrosis was explored in terms of indication expansion**



1) Liver
:NASH/Fibrosis
:PBC/PSC



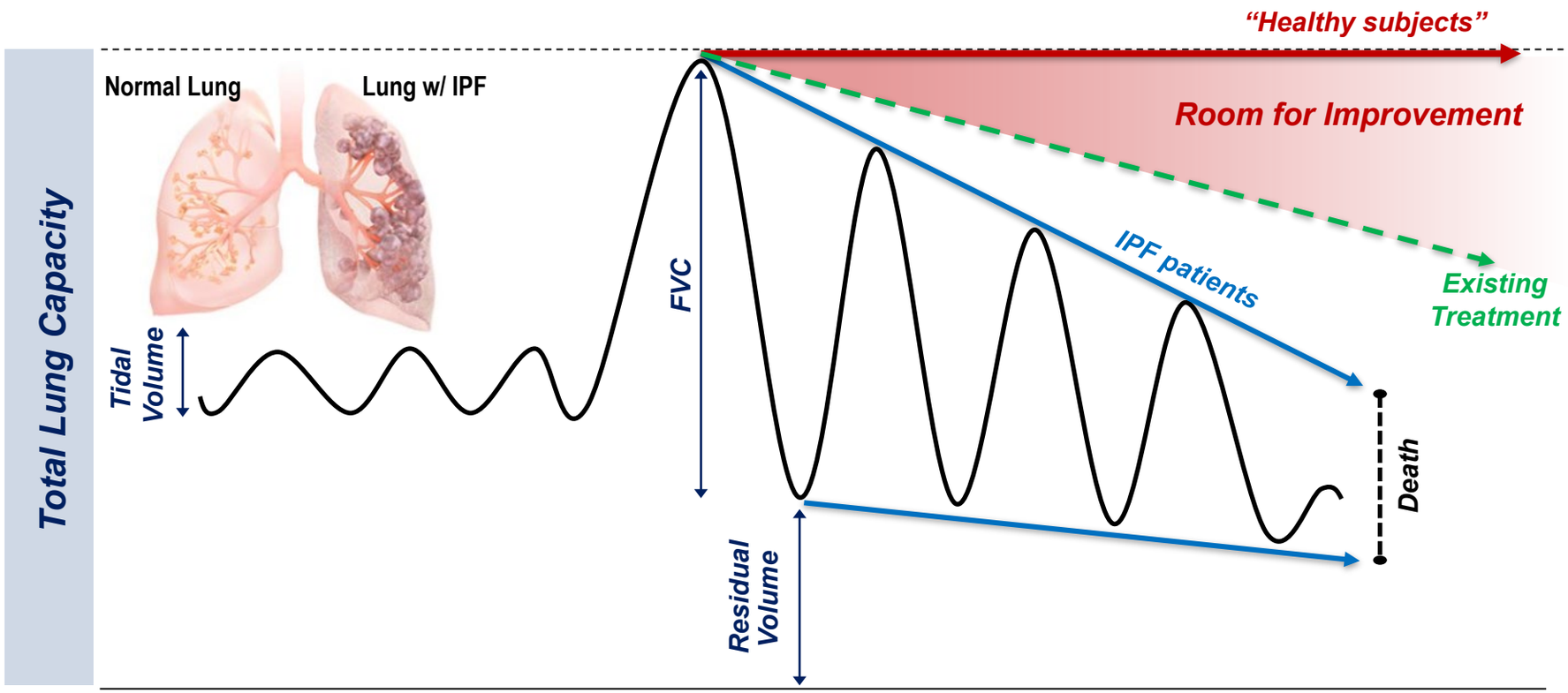
2) Lung
:IPF as our suggestion

Based on the facts below…
1. Lung as another main target tissue of HM15211
2. Robust anti-fibrotic nature of HM15211

Overview of lung function alteration, and predicted targets of HM15211 in IPF

IPF is neither stopped nor reversed and lung function declines while on treatment.
Despite different etiology and pathogenesis, pleiotropic benefits including EMT inhibition and anti-fibrosis suggest medicinal utility of HM15211 for the management of IPF in addition to NASH

Lung Function (FVC) during IPF



Expected Target of HM15211

- ✓ **Fibroblast**
  (MRC-5, human lung fibroblast)
- ✓ **Myofibroblast**
  (LL-29, human IPF patient cell)
- ✓ **Alveolar Epithelium**
  (A549, human alveolar epithelial cell)
- ✓ **Immune Cell**
  (THP-1, human monocyte)

Capillary

Bronchial Epithelium

Please note oral presentation reporting more information about HM15211:
#778: Anti-inflammatory and anti-fibrotic effects of a novel long-acting Glucagon/GIP/GLP-1 triple agonist, HM15211, in TAA induced mouse model of liver injury and fibrosis

Figure 1. Effect of HM15211 on lung function

➢BLM-induced decrease in percent oxygen saturation level (SpO_2) was effectively restored by HM15211 to almost normal control level (93.7% *vs.* 96.2% for normal) at D21, unlike IPF drugs, PIRF (88.0%), NINT (84.9%)

Study design

C57BL/6 mice

Intratracheal administration of **BLM 1.5 U/kg (≈0.9 mg/kg), single**

Drug treatment for 2 wks

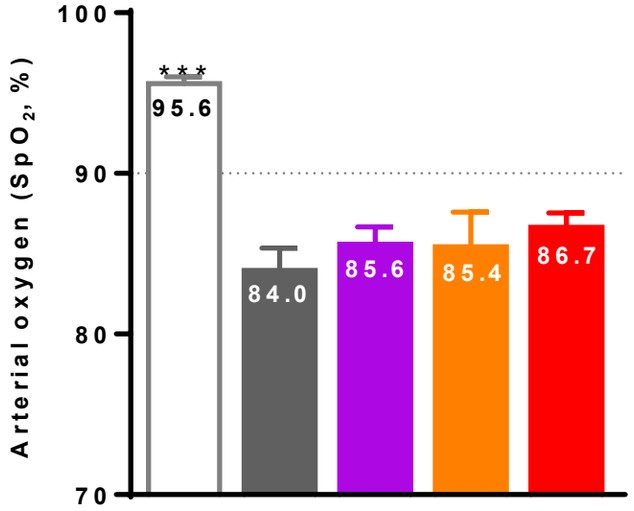
D0 — D7 — D14 — D21 (EoT)

Randomization

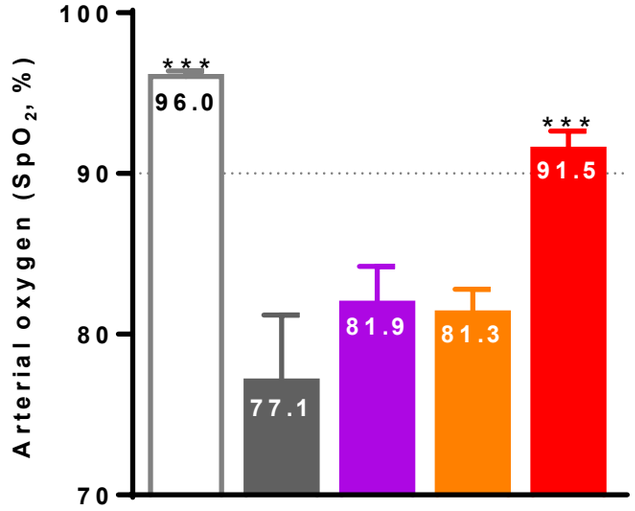
Primary end-point
- Saturated peripheral O_2 (D7 (baseline), D14, D21)

- Saline vehicle
- BLM 1.5 U/kg, vehicle
- BLM 1.5 U/kg, HM15211 141 μg/kg/Q2D
- BLM 1.5 U/kg, Pirfenidone 300 mg/kg/QD
- BLM 1.5 U/kg, Nintedanib 40 mg/kg/QD

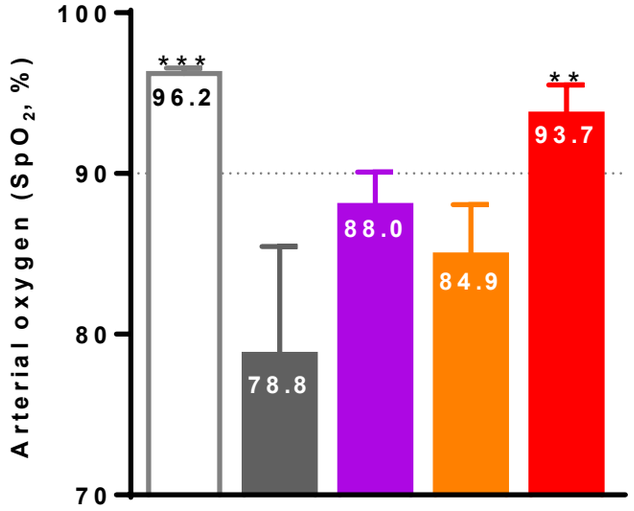
Arterial oxygen (SpO_2, %) at D7



Arterial oxygen (SpO_2, %) at D14



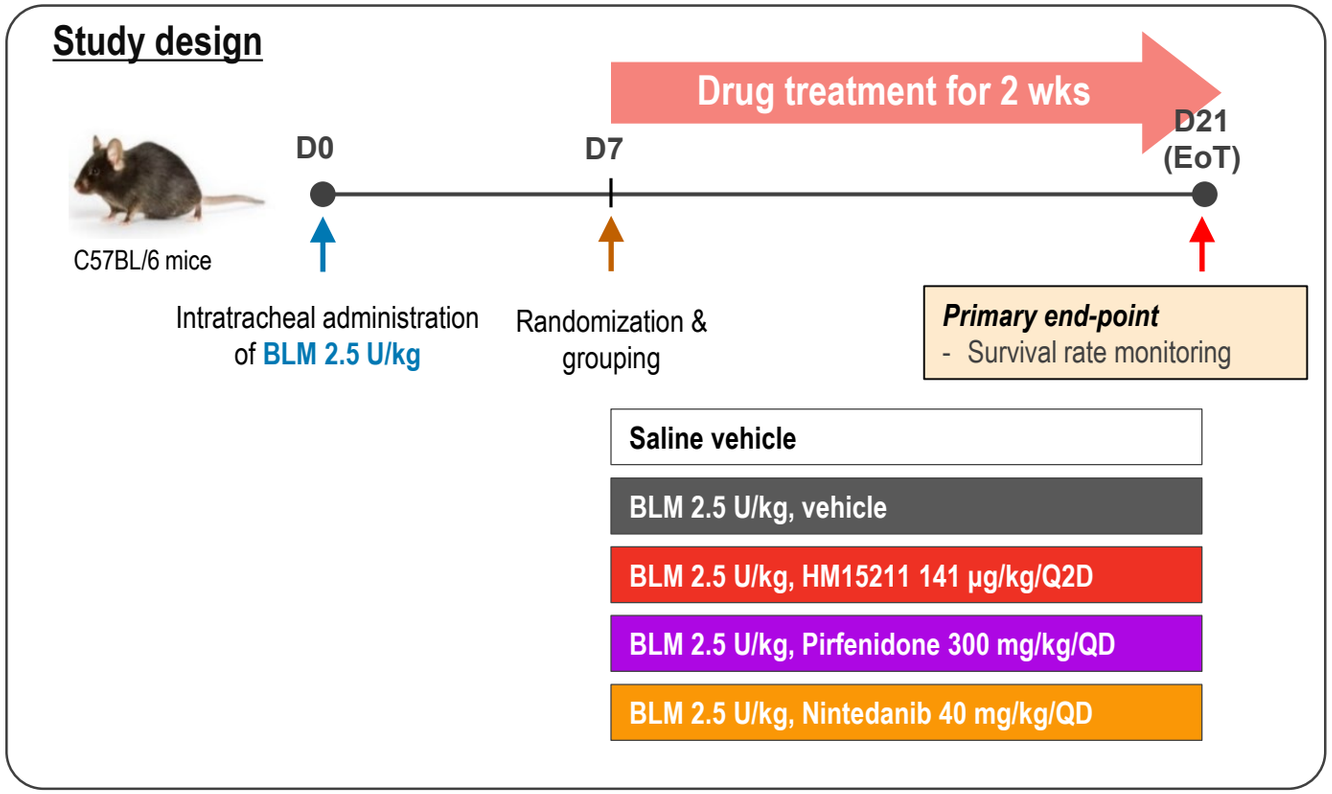
Arterial oxygen (SpO_2, %) at D21



** ~ ***p < 0.01 ~ < 0.001 *vs.* BLM, vehicle by One-way ANOVA

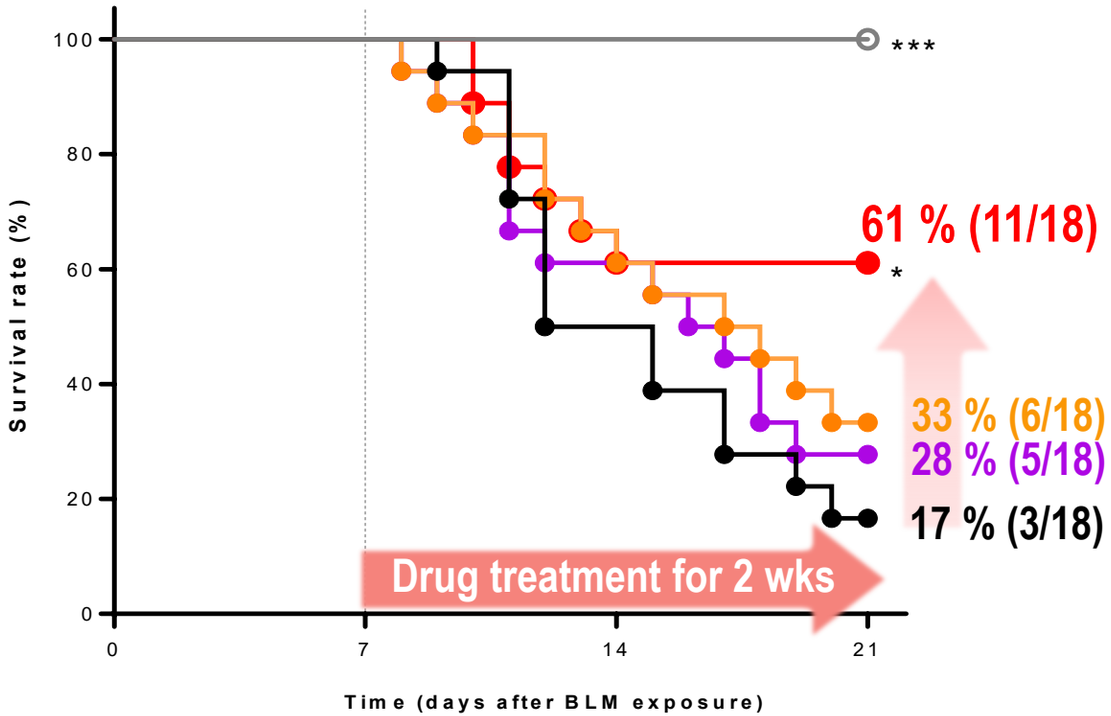
Figure 2. Effect of HM15211 on disease progression and death

➢ 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%), further demonstrating HM15211 could slow disease progression and extend survival in BLM mice



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

Survival rate in 2.5 U/kg BLM mice
(% *vs.* saline vehicle)



- Saline, Vehicle
- BLM 2.5 unit/kg, Vehicle
- BLM 2.5 unit/kg, HM15211 141 μg/kg/Q2D (4 mg/wk in human)
- BLM 2.5 unit/kg, Pirfenidone 300 mg/kg/QD (2,400 mg/day in human)
- BLM 2.5 unit/kg, Nintedanib 40 mg/kg/QD (320 mg/day in human)

Summary & Conclusions

- **HM15211 is a novel long-acting Glucagon/GIP/GLP-1 triple agonist and its therapeutic potential was demonstrated in various animal models of NASH and/or fibrosis**

- **Tissue distribution study indicates that HM15211 is readily distributed to the lung in addition to the liver. These results make us to investigate the potential benefit of HM15211 on fibrotic lung disease with high unmet medical needs such as IPF**

- **In BLM mice, HM15211 improved pulmonary respiratory function and survival rate**

- **Compared to pirfenidone or nintedanib treated groups, HM15211 showed greater improvement effects on all the efficacy measurements in BLM mice**

HM15211 might be a potential therapeutic option for IPF in addition to NASH
Human study should be required for human relevance of these findings

Contact information: seonmyeong.lee@hanmi.co.kr