EFFECT OF BASELINE EMPHYSEMA ON REDUCTION IN FVC DECLINE WITH NINTEDANIB IN THE INPULSIS® TRIALS

Tamera CORTE
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Nintedanib is an investigational agent and is not approved for the treatment of IPF in Australia or NZ; it is approved in the EU and US

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- Advisory board member for AstraZeneca

BACKGROUND

Nintedanib
- An intracellular inhibitor of tyrosine kinases\(^1,2\)
- Targets VEGF, FGF and PDGF receptors\(^1,2\)
- Developed for the treatment of IPF and several types of cancer

Phase II TOMORROW study
- Clinical proof of concept in IPF
- 12 months’ treatment with nintedanib 150 mg bid may reduce lung function decline and acute exacerbations in patients with IPF\(^3\)
- Manageable safety profile\(^3\)

VEGF, vascular endothelial growth factor; FGF, fibroblast growth factor; PDGF, platelet-derived growth factor
INPULSIS®: Two replicate, randomized, double-blind, 52-week, phase III trials

Nintedanib 150 mg bid (n=638)
Placebo (n=423)

Primary endpoint
- Annual rate of decline in forced vital capacity (FVC) (mL/year)

Key secondary endpoints
- Time to first acute exacerbation (investigator-reported) over 52 weeks
- Change from baseline in SGRQ total score over 52 weeks

Safety
- Assessed by clinical and laboratory evaluation and adverse events


KEY INCLUSION CRITERIA

• Age ≥40 years
• Diagnosis of IPF within 5 years of randomization
• Chest HRCT performed within 12 months of screening
• HRCT pattern, and, if available, surgical lung biopsy pattern, consistent with diagnosis of IPF, as assessed centrally by one expert radiologist and one expert pathologist
• FVC ≥50% of predicted value
• DL\textsubscript{CO} 30–79% of predicted value

DL\textsubscript{CO}: carbon monoxide diffusion capacity; FVC, forced vital capacity; HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis.
## ELIGIBILITY CRITERIA BASED ON HRCT

To qualify to enter the INPULSIS® trials if a surgical lung biopsy was not available, criteria A and B and C; or A and C; or B and C had to be met

<table>
<thead>
<tr>
<th>A</th>
<th>Definite honeycomb lung destruction with basal and peripheral predominance</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Presence of reticular abnormality and traction bronchiectasis consistent with fibrosis with basal and peripheral predominance</td>
</tr>
<tr>
<td>C</td>
<td>Atypical features are absent, specifically nodules and consolidation. Ground glass opacity, if present, is less extensive than reticular opacity pattern</td>
</tr>
</tbody>
</table>

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## EMPHYSEMA

*Emphysema was not excluded as in other trials:*

- Presence of emphysema (yes/no) at baseline was determined by qualitative assessment of chest HRCT scans, centrally reviewed by a single radiologist
  - FVC ≥50% of predicted value
  - DL\(_{CO}\) 30–79% of predicted value
  - FEV\(_1\)/FVC >0.7 (pre-bronchodilator)
Aims and methods

Aim
– To investigate the potential impact of emphysema on the effect of nintedanib in patients with IPF

Methods
– Post-hoc subgroup analyses of patients with/without emphysema at baseline were conducted using pooled data from the two INPULSIS® trials
– Subgroup analyses were conducted on the primary and key secondary endpoints

Results
– 412 (39%) patients had emphysema; 644 had no emphysema

Patient disposition

<table>
<thead>
<tr>
<th></th>
<th>No emphysema at baseline</th>
<th>Emphysema at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nintedanib bid</td>
<td>Placebo</td>
</tr>
<tr>
<td>Randomised patients, n</td>
<td>385</td>
<td>259</td>
</tr>
<tr>
<td>Treated patients, n</td>
<td>384</td>
<td>257</td>
</tr>
<tr>
<td>Prematurely discontinued trial medication, n (%)</td>
<td>91 (23.7)</td>
<td>41 (16.0)</td>
</tr>
<tr>
<td>Prematurely discontinued trial medication due to adverse event, n (%)</td>
<td>79 (20.6)</td>
<td>30 (11.7)</td>
</tr>
<tr>
<td>Completed planned observation time, n (%)</td>
<td>328 (85.4)</td>
<td>219 (85.2)</td>
</tr>
</tbody>
</table>

Completed planned observation time = all visits completed or, if patient prematurely discontinued study medication, all visits until week 52 completed. Patients who died were not considered completers.
## Baseline characteristics (1/2)

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<td>Nintedanib 150 mg bid</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>(n=384)</td>
<td>(n=257)</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>67.0 (7.8)</td>
<td>67.9 (8.0)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>277 (72.1)</td>
<td>190 (73.9)</td>
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<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>236 (61.5)</td>
<td>160 (62.3)</td>
</tr>
<tr>
<td>Asian</td>
<td>94 (24.5)</td>
<td>70 (27.2)</td>
</tr>
<tr>
<td>Ex or current smoker, n (%)</td>
<td>235 (61.2)</td>
<td>153 (59.5)</td>
</tr>
<tr>
<td>Time since diagnosis, years, mean (SD)</td>
<td>1.6 (1.3)</td>
<td>1.6 (1.4)</td>
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</table>

## Baseline characteristics (2/2)

<table>
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<td>(n=384)</td>
<td>(n=257)</td>
</tr>
<tr>
<td>FVC, ml, mean (SD)</td>
<td>2579 (748)</td>
<td>2575 (771)</td>
</tr>
<tr>
<td>FVC, % predicted, mean (SD)</td>
<td>78.1 (16.7)</td>
<td>77.0 (18.1)</td>
</tr>
<tr>
<td>FEV1/FVC ratio, %, mean (SD)</td>
<td>82.6 (5.4)</td>
<td>82.5 (5.8)</td>
</tr>
<tr>
<td>DLCO, mmol/min/kPa, mean (SD)</td>
<td>3.9 (1.3)</td>
<td>3.9 (1.2)</td>
</tr>
<tr>
<td>SGRQ total score, mean (SD)*</td>
<td>40.4 (19.7)</td>
<td>40.0 (18.0)</td>
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* n=376 for nintedanib and n=254 for placebo in no emphysema at baseline subgroup; n=248 for nintedanib and n=165 for placebo in emphysema at baseline subgroup.
ANNUAL RATE OF DECLINE IN FVC:
TOTAL POOLED DATA

Treated set (observed cases); mean (SEM) adjusted rate of change in FVC.
bid, twice daily; FVC, forced vital capacity.

Annual rate of decline in FVC

No emphysema at baseline
Emphysema at baseline

Treatment by time by subgroup interaction
p=0.5199
Change from baseline in FVC

Mean (SE) observed change from baseline in FVC (mL)

-300 -250 -200 -150 -100 -50 0 50

No emphysema at baseline – nintedanib
Emphysema at baseline – nintedanib
No emphysema at baseline – placebo
Emphysema at baseline – placebo

Week

0 2 4 6 12 24 36 52

Time to first acute exacerbation

No emphysema at baseline – nintedanib
Emphysema at baseline – nintedanib
No emphysema at baseline – placebo
Emphysema at baseline – placebo
### Proportion of patients with an acute exacerbation and HR for time to first event

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<tr>
<td>Patients with ≥1 acute exacerbation, n (%)</td>
<td>24 (6.3)</td>
<td>20 (7.8)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.82 (0.45, 1.49)</td>
<td>0.36 (0.14, 0.91)</td>
</tr>
<tr>
<td>Treatment by subgroup interaction</td>
<td>p = 0.1449</td>
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### Change from baseline in SGRQ total score at week 52

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</tr>
<tr>
<td></td>
<td>(n=369)</td>
<td>(n=250)</td>
</tr>
<tr>
<td>Adjusted mean (SE) change from baseline in SGRQ total score</td>
<td>4.21 (95% CI: -1.23, 8.66)</td>
<td>5.44 (95% CI: -1.71, 12.56)</td>
</tr>
<tr>
<td>Treatment by subgroup interaction</td>
<td>p=0.9486</td>
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</table>
**Safety**

- 95.5% of patients treated with nintedanib and 89.6% of patients treated with placebo experienced ≥1 adverse event

- The proportion of patients who had ≥1 serious adverse event was similar between the nintedanib (30.4%) and placebo (30.0%) groups

**Conclusions**

- Nintedanib slowed disease progression by reducing the decline in lung function independent of the presence of emphysema at baseline

- Results for the time to first acute exacerbation and change from baseline in SGRQ total score also showed no difference between those with and without emphysema at baseline
Questions for Discussion

- **Real life inclusion criteria** – inclusion of patients with concomitant emphysema previously excluded from IPF trials

- How should we be treating our patients with IPF and concomitant emphysema (CPFE)?
  - Poor prognostic group
  - No real alternative treatment options

Acknowledgements

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