Understanding the mode of action of a drug using Functional Respiratory Imaging (FRI)

Roflumilast Study

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CEO

IPAC-RS/UF Orlando Inhalation Conference
March 20, 2014
• Functional Respiratory Imaging (FRI)
  – FRI outcome parameters
  – Added value in drug and device development

• Clinical Study: Roflumilast in COPD
  – Mode of action
  – Responder phenotype
CHALLENGES IN RESPIRATORY DRUG DEVELOPMENT

Limited sensitivity of current Pulmonary Function Tests (FEV1,...)

Very difficult to demonstrate efficacy of novel compounds, resulting in high number of patients needed in clinical trials

Excessive respiratory drug development cost > $1.5 billion

Difficult to demonstrate bio-equivalence
AIM

- Explain Functional Respiratory Imaging (FRI)
- Demonstrate enhanced sensitivity wrt PFT
- Reduction in # patients required for clinical trials to understand mode of action
- Use clinical trials as a design tool in phase I and II
  - To assess bioequivalence
  - To de-risk phase III
FRI is an imaging biomarkers for respiratory diseases

- What are imaging biomarkers?

According to Wikipedia:

“A biomarker, or biological marker, generally refers to a measured characteristic which may be used as an indicator of some biological state or condition.”
IMAGING BIOMARKERS

Event → Biomarker → Intervention
IMAGING BIOMARKERS

Event → Biomarker → Intervention
Event Biomarker Intervention

FUNCTIONAL RESPIRATORY IMAGING

IMAGING BIOMARKERS
FUNCTIONAL RESPIRATORY IMAGING (FRI)

• High-resolution CT images are converted into patient-specific 3D computer models
FUNCTIONAL RESPIRATORY IMAGING (FRI)

- Computational Fluid Dynamics
- Solving Navier-Stokes equations numerically
- Computational grid
- Boundary conditions

computer model  computational grid  velocity contours
FRI OUTCOME PARAMETERS

CT scan @ Inspiration and Expiration

- Ventilation
- Perfusion & Tissue
- Deposition
CT scan @ Inspiration and Expiration

FRI OUTCOME PARAMETERS

- Ventilation
- Perfusion & Tissue
- Deposition
FRI: VENTILATION
Lobar Volumes

FRC

TLC

FRI: VENTILATION
Airway Volumes

Total Lung Capacity

FRI: VENTILATION

Airway Volumes

Functional Residual Capacity

FRI: VENTILATION
Airway Resistance
CT scan @ Inspiration and Expiration

FRI OUTCOME PARAMETERS

- Ventilation
- Perfusion & Tissue
- Deposition
FRI: PERFUSION

Emphysema
FRI: PERFUSION

Emphysema

FRI: TISSUE

Airway Wall Thickness

FRI OUTCOME PARAMETERS

CT scan @ Inspiration and Expiration

- Ventilation
- Perfusion & Tissue
- Deposition
FRI: DEPOSITION
Aerosol Simulation

DEVICE A

DEVICE B
• Lung deposition increases by 9%
FROM MODE OF ACTION TO CLINICAL BENEFIT

GEOMETRY

PULMONARY FUNCTION

PATIENT’S QUALITY OF LIFE
BENEFIT OF MORE SENSITIVE ENDPOINTS

- Geometry increases
- Pulmonary function increases
- Patient’s quality of life increases

# Confounding factors increases
Required sample size increases
CORRELATION BETWEEN GEOMETRY AND QOL

GEOMETRY

PULMONARY FUNCTION

PATIENT’S QUALITY OF LIFE
Wim Vos, Jan De Backer, Gianluigi Poli, Annick De Volder, Liesbeth Ghys, Cedric Van Holsbeke, Samir Vinchurkar, Lieve De Backer, Wilfried De Backer

Use of novel functional imaging methods for the assessment of long-term changes in small airways of patients treated with extrafine beclomethasone / formoterol

Respiration 2013
CORRELATION BETWEEN GEOMETRY AND PFT

GEOMETRY

PULMONARY FUNCTION

PATIENT’S QUALITY OF LIFE
CORRELATION BETWEEN GEOMETRY AND QOL
Asthma Population (pooled data)

siRaw against FEV1 %
N = 48    Spearman R = -0.65    p<0.001
CORRELATION BETWEEN GEOMETRY AND QOL
COPD Population (pooled data)

siRaw against FEV1 %
N = 92  Spearman R = -0.42  p<0.001
CORRELATION BETWEEN GEOMETRY AND QOL
Asthma Population (pooled data)
CORRELATION BETWEEN GEOMETRY AND QOL
COPD Population (pooled data)
CORRELATION BETWEEN GEOMETRY AND QOL
Asthma Population (pooled data)

Body Plethysmography

FRI

sRaw and siRaw

sRaw [kPa.s] vs. siRaw [kPa.s]

-0.2
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4

Median
25%-75%
Non-Outlier Range
CORRELATION BETWEEN GEOMETRY AND QOL
COPD Population (pooled data)

Body Plethysmography

sRaw and siRaw

FRI

-2 -1 0 1 2 3 4 5 6 7 8
sRaw [kPa.s]

-2 -1 0 1 2 3 4 5 6 7 8 siRaw [kPa.s]

Median
25%-75%
Non-OUTlier Range
SAMPLE SIZE CALCULATION

Asthma Study

Wim Vos, Jan De Backer, Gianluigi Poli, Annick De Volder, Liesbeth Ghys, Cedric Van Holsbeke, Samir Vinchurkar, Lieve De Backer, Wilfried De Backer

Use of novel functional imaging methods for the assessment of long-term changes in small airways of patients treated with extrafine beclomethasone / formoterol

Respiration 2013
Lieve De Backer, Wim Vos, Jan De Backer, Cedric Van Holsbeke, Samir Vinchurkar, Wilfried De Backer

Double blind, placebo controlled crossover study in COPD patients to assess the acute effect of budesonide/formoterol using multi-slice CT and lung function tests

Eur Respir J 2012; 40: 298-305
FRI AS DESIGN TOOL
Adaptive Clinical Trials

TRANSLATIONAL
• PDE 4 inhibitor
• Orally administered
• Label: reduction in exacerbations in severe COPD patients NOT a bronchodilator
• Very long registration procedure
• Costly development (> 10,000 patients)

• Regulatory concern: what is the interaction with ICS/LABA?
  • REACT trial (~2,000 patients), expected end 2014
Physician's Integrity Group Sues FDA Over Roflumilast

By Cyndi Root

Physicians for Integrity in Medical Research (PIMR) filed a complaint, addressed to FDA commissioner Margaret Hamburg, alleging that roflumilast, a drug used to treat chronic obstructive pulmonary disease (COPD), does not work as intended and can cause serious side effects.

Doctors Group Sues FDA, Saying Drug Does More Harm Than Good

By ELIZABETH WARMERDAM

LOS ANGELES (CN) - A physicians group sued the U.S. FDA, seeking revocation of FDA approval of roflumilast, a drug used to treat chronic obstructive pulmonary disease. The drug, whose trade name is Daliresp, may do more harm than good, Physicians for Integrity in Medical Research says in its federal complaint against Food and Drug Administration Commissioner Margaret Hamburg.

The FDA approved roflumilast on Feb. 28, 2011, to treat severe chronic COPD. Roflumilast "does not work as stated" and "does more harm than good to patients with..."
The primary objective of this study is to evaluate the possible use of CT based functional respiratory imaging (FRI) on the phenotyping of severe COPD patients after a 6 month treatment with Roflumilast.

Secondary outcome variables are health related quality of life, lung function tests and exercise tolerance.

Roflumilast on top of triple therapy (ICS/LABA/LAMA)
STUDY DESIGN

- Double blind placebo controlled design
- Block randomization
  - 3 Roflumilast/ 1 placebo
- Inclusion period: ±10 months (jan-oct 2012)
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<th>Baseline*</th>
<th>3 months*</th>
<th>6 months*</th>
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<td>X</td>
<td></td>
<td>X</td>
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<td>Spirometry</td>
<td>X</td>
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<tr>
<td>Body Plethysmography</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Diffusion</td>
<td>X</td>
<td></td>
<td>X</td>
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<tr>
<td>FOT</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>6MWT</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>PRO</td>
<td>X</td>
<td></td>
<td>X</td>
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</tbody>
</table>

*All tests were performed post bronchodilation
**PATIENT POPULATION**

- 41 included COPD GOLD III and IV patients
- 9 drop-outs / 32 evaluable patients

<table>
<thead>
<tr>
<th></th>
<th>Non-dropout</th>
<th>dropout</th>
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<tbody>
<tr>
<td>Length (cm)</td>
<td>167.28±7.83</td>
<td>171.83±9.41</td>
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<tr>
<td>Packyears (years)</td>
<td>53.61±33.69</td>
<td>42.63±20.18</td>
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<tr>
<td>Age (years)</td>
<td>65.41±7.68</td>
<td>68.89±6.66</td>
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<tr>
<td>Weight (kg)</td>
<td>86.53±27.79</td>
<td>78.19±18.31</td>
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<tr>
<td>FVC (%pred)</td>
<td>79.82±19.02</td>
<td>95.29±16.25</td>
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<td>FEV1 (%pred)</td>
<td>42.98±12.04</td>
<td>45.49±9.96</td>
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<td>FEV1/FVC (%)</td>
<td>43.66±12.02</td>
<td>38.18±8.93</td>
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<tr>
<td>RV (%pred)</td>
<td>164.3±34.94</td>
<td>173.63±27.61</td>
</tr>
<tr>
<td>TLC (%pred)</td>
<td>112.13±19.24</td>
<td>122.88±14.56</td>
</tr>
<tr>
<td>FRC (%pred)</td>
<td>142.64±32</td>
<td>157.38±18.3</td>
</tr>
<tr>
<td>Raw (kPas/L)</td>
<td>0.74±0.31</td>
<td>0.69±0.16</td>
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<tr>
<td>sRaw (kPas)</td>
<td>3.7±1.83</td>
<td>3.84±1.2</td>
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<td>LCI (-)</td>
<td>8.96±1.5</td>
<td>8.84±0.84</td>
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<tr>
<td>N2 washout time (min)</td>
<td>4.87±2.36</td>
<td>4.76±1.91</td>
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<tr>
<td>6MWT (m)</td>
<td>371.26±109.73</td>
<td>373.38±66.63</td>
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</table>
• 32 evaluable patients
• 23 treated with Roflumilast on top of ICS/LABA/LAMA
• 9 treated with placebo on top of ICS/LABA/LAMA

<table>
<thead>
<tr>
<th></th>
<th>Roflumilast</th>
<th>placebo</th>
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<tbody>
<tr>
<td>Length (cm)</td>
<td>166.2±6.44</td>
<td>170.06±10.56</td>
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<tr>
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<td>53.13±35.57</td>
<td>54.83±30.24</td>
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<tr>
<td>Age (years)</td>
<td>63.61±7.38</td>
<td>70±6.76</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>84.08±28.58</td>
<td>92.81±26.18</td>
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<tr>
<td>FVC (%pred)</td>
<td>79.76±21.08</td>
<td>79.97±13.43</td>
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<tr>
<td>FEV1 (%pred)</td>
<td>41.3±12.17</td>
<td>47.28±11.19</td>
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<td>FEV1/FVC (%)</td>
<td>42.5±12.62</td>
<td>46.61±10.41</td>
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<tr>
<td>RV (%pred)</td>
<td>171.32±35.31</td>
<td>146.36±28.26</td>
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<tr>
<td>TLC (%pred)</td>
<td>114.44±21.39</td>
<td>106.22±11.02</td>
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<tr>
<td>FRC (%pred)</td>
<td>147.22±33.72</td>
<td>130.94±25.07</td>
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<tr>
<td>Raw (kPas/L)</td>
<td>0.77±0.3</td>
<td>0.67±0.35</td>
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<tr>
<td>sRaw (kPas)</td>
<td>3.97±1.96</td>
<td>3±1.26</td>
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<tr>
<td>LCI (-)</td>
<td>8.87±1.33</td>
<td>9.16±1.94</td>
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<tr>
<td>N2 washout time (min)</td>
<td>5.48±2.51</td>
<td>3.46±1.16</td>
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<tr>
<td>6MWT (m)</td>
<td>357.53±90.02</td>
<td>403.88±148.84</td>
</tr>
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</table>
• Significant improvement in FEV1 in Roflumilast group (+66ml) compared to drop in placebo (-59ml)

\[ p = 0.006 \]

\[ p = 0.01 \]

\[ p = 0.052 \]
• 8 patients (35%) in the Roflumilast group have a FEV1 response > 120ml* (+ 186 ml on average)
• Responders are the patients who feel at baseline significantly worse after 6MWT compared to non-responders in terms of Borg score

*Quality and reproducibility of spirometry in COPD patients in a randomized trial (UPLIFT).
ROFLUMILAST RESPONDERS IN TERMS OF FEV1

- 8 patients (35%) in the Roflumilast group have a FEV1 response > 120ml* (+ 186 ml on average)
- Responders are the patients who feel at baseline significantly worse after 6MWT compared to non-responders in terms of Borg score

*Quality and reproducibility of spirometry in COPD patients in a randomized trial (UPLIFT).
Roflumilast reduces regional hyperinflation in responders
ROFLUMILAST RESPONDERS IN TERMS OF HYPERINFLATION

- Regional hyperinflation @ FRC

Both subjects are female, 1.70m
ROFLUMILAST RESPONDERS IN TERMS OF HYPERINFLATION

- FRC lobes reduce significantly in volume for the Daxas responders (-4.88 %p) as compared to the non-responders (+3.47 %p) and placebo (+8.28 %p)

![Graph showing the change in FRC volume as compared to the baseline. The graph compares responders, non-responders, and placebo groups. The p-values for the comparison are indicated: p=0.025, p=0.001, p=0.16.]
ROFLUMILAST RESPONDERS IN TERMS OF HYPERINFLATION

- Regional hyperinflation change @ FRC in Roflumilast responder

Baseline: 164%p, 175%p, 369%p, 195%p
6m: 184%p, 174%p, 167%p, 217%p, 350%p, 219%p, 193%p
• Roflumilast responders improve 6MWT distance (+53.5 m)
HYPOTHESIS 1

Roflumilast reduces regional hyperinflation in responders
HYPOTHESIS 2

Roflumilast improves efficacy of ICS/LABA/LAMA in responders
ROFLUMILAST RESPONDERS IN TERMS OF BRONCHODILATION

- Roflumilast changes internal airflow distribution and deposition efficacy of ICS/LABA/LAMA
### ROFLUMILAST RESPONDERS IN TERMS OF BRONCHODILATION

#### Lobes FRC

<table>
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<tr>
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<tbody>
<tr>
<td>RUL</td>
<td>0.967</td>
<td>17.55</td>
<td>164.17</td>
<td>HHH</td>
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<tr>
<td>RML</td>
<td>0.452</td>
<td>8.19</td>
<td>174.97</td>
<td>HHH</td>
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<tr>
<td>RLL</td>
<td>1.515</td>
<td>27.49</td>
<td>218.54</td>
<td>HHH</td>
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<td>1.233</td>
<td>22.37</td>
<td>183.96</td>
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<tr>
<td>LLL</td>
<td>1.346</td>
<td>24.41</td>
<td>217.40</td>
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#### Lobes TLC

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<td>26.27</td>
<td>118.55</td>
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<td>1.484</td>
<td>22.06</td>
<td>133.45</td>
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<tr>
<td>LLL</td>
<td>1.724</td>
<td>25.62</td>
<td>126.60</td>
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#### Baseline Distribution

<table>
<thead>
<tr>
<th>Lobes</th>
<th>Distribution[% Total]</th>
<th>Normal range[% Total]</th>
<th>Comment</th>
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<td>1.55</td>
<td>[2.95, 8.57]</td>
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<tr>
<td>RML</td>
<td>7.56</td>
<td>[2.55, 3.70]</td>
<td>L</td>
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<td>RLL</td>
<td>20.65</td>
<td>[13.75, 22.93]</td>
<td>N</td>
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<tr>
<td>LUL</td>
<td>31.16</td>
<td>[24.87, 33.61]</td>
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#### Post Distribution

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<td>184.60</td>
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<td>1.356</td>
<td>24.73</td>
<td>219.01</td>
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<td>1.757</td>
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#### Normal range[% Total]

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<th>Volume[% Total]</th>
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<td>RLL</td>
<td>4.20</td>
<td>N</td>
</tr>
<tr>
<td>LUL</td>
<td>17.48</td>
<td>N</td>
</tr>
<tr>
<td>LLL</td>
<td>31.08</td>
<td>N</td>
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</table>
Does airflow redistribution lead to differences in aerosol deposition patterns in the responders?
ROFLUMILAST RESPONDERS IN TERMS OF BRONCHODILATION

- FRI can determine aerosol deposition patterns:
Roflumilast responder

- Seretide Diskus (LABA/ICS)
  - 8% more deep lung deposition
  - 38% more deposition in the lower lobes
ROFLUMILAST RESPONDERS IN TERMS OF BRONCHODILATION

Roflumilast responder

- Spiriva Respimat (LAMA)
  - 6% more deep lung deposition
  - 37% more deposition in the lower lobes
ROFLUMILAST RESPONDERS IN TERMS OF BRONCHODILATION

- Significant improvement in iVaw for the Roflumilast responders (+8.5%)
ROFLUMILAST RESPONDERS IN TERMS OF BRONCHODILATION

- Significant improvement in iRaw for the Roflumilast responders (-30%)

P=0.002
ROFLUMILAST RESPONDERS IN TERMS OF BRONCHODILATION

- Significant improvement in iVaw for the ROFLUMILAST responders
• No improvement in iVaw for the ROFLUMILAST non-responders
Roflumilast improves efficacy of ICS/LABA/LAMA in responders
MODE OF ACTION OF ROFLUMILAST IN RESPONDERS

- Orally administered Roflumilast reaches areas undertreated with inhaled medication
- Reduction in regional hyperinflation
- Redistribution of internal airflow distribution
- Redistribution of inhaled ICS/LABA/LAMA
- Additional improvement in FEV1, exercise tolerance,...
MODE OF ACTION OF ROFLUMILAST IN RESPONDERS

MoA Roflumilast points to regional hyperinflation

Label of Roflumilast: reduction in exacerbations

What is link between regional hyperinflation and exacerbations
COPD EXACERBATIONS

- Pilot study in patients with exacerbation
- FRI during exacerbation
- FRI after recovery

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<th>Lobar Volume</th>
<th>Change in FRC (%)</th>
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<td>-0.0%</td>
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<tr>
<td>RLL</td>
<td>-14.3%</td>
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<tr>
<td>LUL</td>
<td>-11.7%</td>
</tr>
<tr>
<td>LLL</td>
<td>-12.9%</td>
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</table>
• Roflumilast improves the patient compared to placebo
• Roflumilast group has responders and non-responders
• Study provided hypothesis for the mode of action of response and for the phenotype of the responders

• Interaction between systemic and inhaled drugs is of paramount importance.

CONCLUSIONS

Wilfried De Backer, Wim Vos, Cedric Van Holsbeke, Samir Vinchurkar, Rita Claes, Annemie Hufkens, Paul M. Parizel, Lieven Bedert, Jan De Backer

The effect of Roflumilast in addition to LABA/LAMA/ICS treatment in COPD patients.

Eur Respir J 2014 (in press)
CONCLUSIONS

• FRI is more sensitivity compare to standard PFT

• Reduction in # patients required for clinical trials to understand mode of action

• Use clinical trials as a design tool in phase I and II
  • To de-risk phase III (eg Roflumilast trial)
  • To assess bioequivalence
BIO-EQUIVALENCE USING FRI

CFD-based deposition

CT-based bronchodilation

CFD-based resistance change

Submitted for ERS 2014
• Broader implementation of FRI in phase I and II clinical studies

• FRI as surrogate endpoint for (rare) lung diseases
  • Idiopathic pulmonary fibrosis
  • Cystic Fibrosis
  • Alpha 1 antitrypsin deficiency
  • Lung transplantation
  • Bronchiolitis obliterans

• FRI to assess bio-equivalence
• Cystic fibrosis patients
• Aim: to evaluate whether 2 year CT follow up of CF patients would provide added insight on disease progression
  – 10 CF patients
  – 5 males/ 5 females
  – 14±6 years at inclusions
  – Low dose CT scan at FRC and TLC
  – Baseline scan and after 2 years
BIOMARKER – DISEASE PROGRESSION TRACKING
CF CASE

Patient 3

Patient 4
ITmoc study

- Patient 5
• Patient 5

Drop in FEV1 only after several months – while FRI was able to predict decrease in lung function way earlier.
Regional concentration relative to a minimal inhibitory concentration threshold for inhaled antibiotics.

Relative AZLI concentration as compared to 10 x MIC90 [-]

- 100.0
- 80.0
- 60.0
- 40.0
- 20.0
- 10.0
- 8.0
- 6.0
- 4.0
- 2.0
- 1.0
- 0.9
- 0.8
- 0.7
- 0.6
- 0.5
- 0.4
- 0.3
- 0.2
- 0.1
- 0.0
FRI: DEPOSITION
Aerosol Simulation

Previous Medication Fine Particles

Beclomethasone/Formoterol Extra-fine Particles
FRI: DEPOSITION
Aerosol Simulation
Previous Medication Fine Particles

Beclomethasone/Formoterol Extra-Fine Particles

Vinchurkar et al. Inhalation Toxicology (2012) 24(2): 81-8
Lung deposition increased by 9%
FRI: DEPOSITION

Aerosol Simulation

Distal lung deposition (p=0.005)

- Previous Medication
  - Fine Particles
- Becl/Form
  - Extra-Fine Particles

- Median
- 25%-75%
- Non-Outlier Range
- Outliers
- Extremes
FRI: DEPOSITION
Aerosol Simulation

![Graph showing iRaw (p=0.01)]

- **iRaw (p=0.01)**

  - [KPa/s/L]
    - 0.16
    - 0.14
    - 0.12
    - 0.10
    - 0.08
    - 0.06
    - 0.04
    - 0.02
    - 0.00

  - **Previous Medication Fine Particles**
  - **Becl/Form Extra-Fine Particles**

  - **Median**
  - **25%-75%**
  - **Non- Outlier Range**
  - **Outliers**
  - **Extremes**
Radiation dose reduction in CF patients, how low can you go?

Breath hold at TLC
Lung height = 15 cm
100kV
163.16mAs
4mSv
Natural contrast of air

Lung height = 15 cm
80kV
67.26mAs
1.3mSv
Iterative reconstruction

Lung height = 14 cm
80kV
4mAs
0.08mSv
Free breathing