TOwards a Revolution in COPD Health – the TORCH trial
COPD is the only major cause of death that has increased significantly in recent years

Change in age-adjusted death rate in USA, from 1965 to 1998 (%)

-59 CHD
-64 Stroke
-35 CVD
+163 COPD
-7 All other causes

COPD = chronic obstructive pulmonary disease
CHD = coronary heart disease
CVD = cerebrovascular disease

Adapted from: www.copdgold.com
COPD is projected to be the third biggest killer by 2020

<table>
<thead>
<tr>
<th>Disease</th>
<th>1990</th>
<th>2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic heart disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower respiratory infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoeal disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perinatal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuberculosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Road traffic accident</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung cancer</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Murray & Lopez 1997
Rationale for TORCH: Post-hoc analysis of ISOLDE data suggest a positive survival trend for FP

Waterhouse et al. Eur Respir J 1999

ISOLDE = Inhaled Steroids in Obstructive Lung Disease in Europe study
FP = fluticasone propionate

p=0.069

Cumulative survival

Time from start of inhaled study treatment (days)
TORCH Design and Methodology
TORCH: study design

2 week run-in

SFC 50/500 µg bd  (N=1533)

FP 500 µg bd  (N=1534)

SAL 50 µg bd  (N=1521)

Placebo  (N= 1524)

3-year study duration

Worldwide participation in TORCH
42 countries
TORCH: main objectives

Primary objective
- The effect of SFC 50/500 µg vs placebo on all-cause mortality over 3 years in patients with moderate-to-severe COPD

Secondary objectives
- The effect of SFC 50/500 µg on the rate of moderate and severe exacerbations
- The effect of SFC 50/500 µg on health status (SGRQ)

SGRQ = St. George’s Respiratory Questionnaire

Vestbo et al. Eur Respir J 2004
Calverley et al. NEJM 2007
Study population: inclusion criteria

- Established history of COPD (ERS definition)
- Aged 40–80 years inclusive
- Smoking history ≥ 10 pack years
- Reversibility < 10% in predicted FEV₁
- FEV₁ < 60% predicted (pre-bronchodilator)
- FEV₁/FVC ratio ≤ 70%
- Able to use Diskus/Accuhaler

ERS = European Respiratory Society
FVC = Forced Vital Capacity

Vestbo et al. Eur Respir J 2004
Calverley et al. NEJM 2007
Safety assessments

- Adverse events
- Concurrent illnesses
- Bone fractures – traumatic and non-traumatic
- Oropharyngeal examination

Vestbo et al. Eur Respir J 2004
Safety sub-study

- Conducted at 88 sites in the USA
- BMD – measured at two anatomical sites
  - Total hip
  - L1–L4 region of spine
- Ophthalmic exams for cataracts and glaucoma

Assessments

- Prior to first dose of study drug
- Annually (visits 6, 11 and 16)

Vestbo et al. Eur Respir J 2004
Calverley et al. NEJM 2007
Steering Committee (SC)

- Worked with the Sponsor to design and implement the study
- Worked with the Sponsor to ensure proper study conduct and conformance with the protocol
- Made recommendations to the sponsor on the basis of information and recommendations from SEDMC
- Publications, presentations and international meetings
Safety and Efficacy Data Monitoring Committee (SEDMC)

- Primary data and safety advisory group for the study
- Regularly reviewed serious adverse events and any safety issues emerging during the study
- Reviewed the interim analyses performed on the primary efficacy variable (all-cause mortality for SFC 50/500 μg vs placebo)
- Made recommendations to the Steering Committee regarding continuation, modification or otherwise, of the study
Planned interim analyses

In addition to the final analysis, two interim analyses were planned

- If overwhelming efficacy had been observed, the study could have been terminated at either interim analysis
- Timings of the interim analyses were based on the number of observed deaths
- Statistically, each interim analysis increases the chance of falsely rejecting the null hypothesis of no difference (‘Type 1 error’)

Need to preserve Type I error ($\alpha$) of 5% overall

- Type I error is inflated if no adjustment to p-value
- Therefore, adjust p-value at the final analysis

This adjustment was applied to the primary endpoint only
Assessment of mortality by the Clinical Endpoint Committee (CEC)

- The CEC independently reviewed all fatal events (post randomisation) occurring during the course of the study.
- All available documentation (e.g. clinical records, death certificates and site investigator narratives) was reviewed in order to assign a primary cause of death.
- The CEC also determined whether the death was COPD-related.
- Deaths were COPD-related if:
  - COPD was the primary cause of death OR
  - Terminal event is hypercapnic respiratory failure or failure to be liberated from a ventilator OR
  - Patient would probably have survived terminal event if COPD not present.
Results: Demography and Disposition
### Populations

<table>
<thead>
<tr>
<th>Population</th>
<th>Placebo</th>
<th>SAL</th>
<th>FP</th>
<th>SFC</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety</td>
<td>1544</td>
<td>1542</td>
<td>1552</td>
<td>1546</td>
<td>6184</td>
</tr>
<tr>
<td>Intent-to-treat (ITT) efficacy</td>
<td>1524</td>
<td>1521</td>
<td>1534</td>
<td>1533</td>
<td>6112</td>
</tr>
</tbody>
</table>

Calverley et al. NEJM 2007
## Demographics

<table>
<thead>
<tr>
<th>ITT</th>
<th>N=6112</th>
<th>Mean (sd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>65 (8)</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>76%</td>
<td></td>
</tr>
<tr>
<td>Current smokers</td>
<td>43%</td>
<td></td>
</tr>
<tr>
<td>Pack years</td>
<td>49 (27)</td>
<td></td>
</tr>
<tr>
<td>% pred baseline FEV$_1$ (post bronc)</td>
<td>44 (13)</td>
<td></td>
</tr>
<tr>
<td>% pred reversibility</td>
<td>3.7 (3.7)</td>
<td></td>
</tr>
<tr>
<td>≥1 exacerbations in previous year</td>
<td>57%</td>
<td></td>
</tr>
</tbody>
</table>

Calverley *et al.* NEJM 2007
**Premature study drug discontinuation**

Probability of withdrawal (%)

![Graph showing probability of withdrawal over time for different groups.]

Time to withdrawal from study medication (weeks)

- **Placebo**: 1524, 1141, 1005, 640
- **SALM**: 1521, 1240, 1093, 717
- **FP**: 1534, 1247, 1112, 681
- **SFC**: 1533, 1296, 1164, 758

Statistical comparisons: SALM/FP, SAL & FP vs placebo p < 0.001; SALM/FP vs SAL p = 0.048; SALM/FP vs FP p = 0.01

Vertical bars are standard errors

Calverley *et al.* NEJM 2007
## Characteristics of patients withdrawing early from the study

<table>
<thead>
<tr>
<th>Time on treatment (placebo arm)</th>
<th>Baseline mean SGRQ Total Score</th>
<th>Baseline mean FEV₁ (L)</th>
<th>Exacerbations* mean rate per annum</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 months (n=275)</td>
<td>52</td>
<td>1.09</td>
<td>2.4</td>
</tr>
<tr>
<td>6-12 months (n=127)</td>
<td>53</td>
<td>1.16</td>
<td>1.8</td>
</tr>
<tr>
<td>12-24 months (n=145)</td>
<td>49</td>
<td>1.20</td>
<td>1.5</td>
</tr>
<tr>
<td>24-30 months (n=63)</td>
<td>48</td>
<td>1.23</td>
<td>1.4</td>
</tr>
<tr>
<td>&gt;30 months (n=914)</td>
<td>47</td>
<td>1.29</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Placebo patients with the poorest health status, worst lung function and more frequent exacerbations withdrew earlier.

Placebo patients were more likely to withdraw early from treatment compared with SFC patients, which may lead to conservative estimates of treatment benefit.

* Moderate/severe exacerbations, on-treatment

Jones et al. AJRCCM 2007 (abstract)
Results: Mortality
Primary analysis: all-cause mortality at 3 years

Probability of death (%) vs. Time to death (weeks)

HR 0.825, p=0.052
17.5% risk reduction
2.6% absolute reduction

SFC 12.6%
Placebo 15.2%

Number alive:
- SFC: 1524, 1464, 1399, 1293
- Placebo: 1533, 1487, 1426, 1339

Vertical bars are standard errors

Calverley et al. NEJM 2007

June 2007
Supportive analysis: All-cause mortality at 3 years - Cox’s proportional hazards

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N = 1524)</th>
<th>SFC (N = 1533)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of deaths</td>
<td>231</td>
<td>193</td>
</tr>
<tr>
<td>Percentage of deaths by 3 years</td>
<td>15.2</td>
<td>12.6</td>
</tr>
<tr>
<td>HR (95% CI)†</td>
<td>0.811 (0.670, 0.982)</td>
<td></td>
</tr>
<tr>
<td>p-value†</td>
<td>0.031</td>
<td></td>
</tr>
</tbody>
</table>

†Cox's proportional hazards model estimate at mean age, FEV₁, body mass index and proportional coefficients for smoking status, gender and region

Calverley et al. NEJM 2007
All-cause mortality at 3 years

Probability of death (%)

Time to death (weeks)

Number alive

Placebo 1524 1464 1399 1293
SALM 1533 1487 1426 1339
FP 1521 1481 1417 1316
SFC 1534 1487 1409 1288

Vertical bars are standard errors

Calverley et al. NEJM 2007
All-cause mortality: Interactions with treatment*

There were no statistically significant interactions (all \( p > 0.120 \)) by baseline characteristics including

- Baseline FEV\(_1\) by GOLD stage (<30%, 30-%<50%, >50% FEV\(_1\))
- Smoking status
- Age
- Gender
- Region

No statistically significant interactions indicates there is no evidence that SFC is more effective in one subgroup than in any other

*Cox’s Proportional Hazards Analysis of all-cause mortality at 3 years interaction tests

Calverley et al. NEJM 2007
COPD-related mortality by 3 years

Probability of death (%)

Time to death (weeks)

Number alive

Placebo 1524 1499 1476 1433
SALM 1533 1513 1490 1460
FP 1521 1502 1475 1428
SFC 1534 1515 1485 1428

Vertical bars are standard errors

Calverley et al. NEJM 2007
Overall causes of death as adjudicated by the Clinical Endpoint Committee

- Cardiac: 27%
- Cancer: 21%
- Respiratory: 35%
- Other: 10%
- Unknown: 7%

Figuren er tegnet av GSK på bakgrunn av data i studien

Calverley et al. NEJM 2007
Cause of death on treatment (adjudicated by CEC)

Deaths (%)

- Cardiovascular
- Pulmonary
- Cancer
- Other
- Unknown

Placebo
SFC

Calverley et al. NEJM 2007

Figuren er tegnet av GSK på bakgrunn av data i studien

June 2007
Secondary and other efficacy endpoints
Efficacy endpoints

- Mortality benefits are important, but may be of less relevance if other endpoints are not met

- Key goals of COPD management include:
  - Exacerbations
  - Quality of Life
  - Lung function
Rate of moderate and severe exacerbations over three years

Mean number of exacerbations/year

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo</th>
<th>SALM</th>
<th>FP</th>
<th>SFC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number</td>
<td>1.13</td>
<td>0.97*</td>
<td>0.93*</td>
<td>0.85**‡‡</td>
</tr>
</tbody>
</table>

25% reduction

*p < 0.001 vs placebo; †p = 0.002 vs SALM; ‡p = 0.024 vs FP

Calverley et al. NEJM 2007

*Figuren er tegnet av GSK på bakgrunn av data i studien
Rate of exacerbations requiring systemic corticosteroids over three years

Mean number of exacerbations/year

- Placebo: 0.80
- SALM: 0.64*
- FP: 0.52*
- SFC: 0.46**

43% reduction

*p < 0.001 vs placebo; †p < 0.001 vs SALM; ‡p = 0.017 vs FP

Calverley et al. NEJM 2007

Figuren er tegnet av GSK på bakgrunn av data i studien
Exacerbations requiring hospitalisation over three years

Mean number of exacerbations/year

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean number of exacerbations/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.19</td>
</tr>
<tr>
<td>SALM</td>
<td>0.16*</td>
</tr>
<tr>
<td>FP</td>
<td>0.17</td>
</tr>
<tr>
<td>SFC</td>
<td>0.16†</td>
</tr>
</tbody>
</table>

* p = 0.016 vs placebo; † p = 0.028 vs placebo

Calverley et al. NEJM 2007

C/07/170  Figuren er tegnet av GSK på bakgrunn av data i studien

June 2007
SGRQ total score

Adjusted mean change SGRQ total score (units)

-5  -4  -3  -2  -1  0  1  2  3

0  24  48  72  96  120  156

Time (weeks)

Placebo  SALM  FP  SFC

Number of subjects

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>SALM</th>
<th>FP</th>
<th>SFC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1149</td>
<td>1148</td>
<td>1155</td>
<td>1133</td>
<td></td>
</tr>
<tr>
<td>854</td>
<td>906</td>
<td>942</td>
<td>941</td>
<td></td>
</tr>
<tr>
<td>781</td>
<td>844</td>
<td>848</td>
<td>873</td>
<td></td>
</tr>
<tr>
<td>726</td>
<td>807</td>
<td>807</td>
<td>814</td>
<td></td>
</tr>
<tr>
<td>675</td>
<td>723</td>
<td>751</td>
<td>773</td>
<td></td>
</tr>
<tr>
<td>635</td>
<td>701</td>
<td>686</td>
<td>731</td>
<td></td>
</tr>
<tr>
<td>569</td>
<td>634</td>
<td>629</td>
<td>681</td>
<td></td>
</tr>
</tbody>
</table>

*p = 0.057 vs placebo; †p < 0.001 vs placebo; ††p < 0.001 vs placebo, SALM and FP; vertical bars are standard errors

Calverley et al. NEJM 2007
SFC significantly improved health status over placebo* across all domains of the St George’s Respiratory Questionnaire (all p<0.001)

- Symptoms: -3.6 units
- Activity: -2.8 units
- Impact: -3.2 units

* Average improvement over the study period

Jones et al. Chest 2006
Change in health status

Category of change
- Improved (≥ 4 units better)
- No change (≤ 4 units better or worse)
- Deteriorated (≥ 4 units worse)

58% patients receiving SFC maintained or improved health status compared with 42% on placebo (p<0.001), 49% on SAL and 52% on FP (p≤0.006)
**Post-bronchodilator FEV$_1$**

Adjusted mean change FEV$_1$ (mL)

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>Placebo</th>
<th>SALM</th>
<th>FP</th>
<th>SFC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1524</td>
<td>1521</td>
<td>1534</td>
<td>1533</td>
</tr>
<tr>
<td>24</td>
<td>1248</td>
<td>1317</td>
<td>1346</td>
<td>1375</td>
</tr>
<tr>
<td>48</td>
<td>1128</td>
<td>1218</td>
<td>1230</td>
<td>1281</td>
</tr>
<tr>
<td>72</td>
<td>1049</td>
<td>1127</td>
<td>1157</td>
<td>1180</td>
</tr>
<tr>
<td>96</td>
<td>979</td>
<td>1054</td>
<td>1078</td>
<td>1139</td>
</tr>
<tr>
<td>120</td>
<td>906</td>
<td>1012</td>
<td>1006</td>
<td>1073</td>
</tr>
<tr>
<td>156</td>
<td>819</td>
<td>934</td>
<td>908</td>
<td>975</td>
</tr>
</tbody>
</table>

* $p < 0.001$ vs placebo; † $p < 0.001$ vs SALM and FP

Calverley et al. NEJM 2007
# Rate of decline in FEV<sub>1</sub>: Treatment effect

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N = 1524)</th>
<th>SALM (N = 1521)</th>
<th>FP (N = 1534)</th>
<th>SFC (N = 1533)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>1,261</td>
<td>1,334</td>
<td>1,356</td>
<td>1,392</td>
</tr>
<tr>
<td>Baseline FEV&lt;sub&gt;1&lt;/sub&gt; (L)</td>
<td>1.26</td>
<td>1.23</td>
<td>1.23</td>
<td>1.24</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment effect</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SFC vs placebo (mL)</td>
<td>16</td>
<td>(8, 25)</td>
</tr>
<tr>
<td>SAL vs placebo (mL)</td>
<td>13</td>
<td>(4, 22)</td>
</tr>
<tr>
<td>FP vs placebo (mL)</td>
<td>13</td>
<td>(4, 22)</td>
</tr>
</tbody>
</table>

Celli *et al.* AJRCCM 2007 (abstract)
Summary of efficacy results

- There was a trend towards improved survival with SFC compared with control

- This was supported by
  - Significantly fewer exacerbations compared with components or placebo
  - Significantly fewer hospitalisations compared with placebo
  - Significant improvements in health status superior to components and placebo
  - Significant improvements in lung function superior to components and placebo
  - Significant reduction in decline in lung function compared with placebo

1. Calverley et al. NEJM 2007
3. Celli et al AJRCCM 2007
Results: Safety
### Exposure to study medication

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N = 1544)</th>
<th>SAL (N = 1542)</th>
<th>FP (N = 1552)</th>
<th>SFC (N = 1546)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total treatment exposure (years)</td>
<td>3,278</td>
<td>3,531</td>
<td>3,555</td>
<td>3,700</td>
</tr>
<tr>
<td>Active treatment-years’ exposure (ratio to placebo)</td>
<td>1.08</td>
<td>1.08</td>
<td>1.13</td>
<td></td>
</tr>
</tbody>
</table>

Calverley et al. NEJM 2007
### Most common reported AEs which started during treatment: Rate per treatment year

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo (N = 1544)</th>
<th>SALM (N = 1542)</th>
<th>FP (N = 1552)</th>
<th>SFC (N = 1546)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD exacerbations</td>
<td>0.92</td>
<td>0.76</td>
<td>0.78</td>
<td>0.67</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>0.10</td>
<td>0.08</td>
<td>0.09</td>
<td>0.11</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>0.09</td>
<td>0.09</td>
<td>0.10</td>
<td>0.10</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0.04</td>
<td>0.04</td>
<td>0.07</td>
<td>0.07</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>Headache</td>
<td>0.08</td>
<td>0.06</td>
<td>0.06</td>
<td>0.05</td>
</tr>
<tr>
<td>Back pain</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>0.03</td>
<td>0.03</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>Cough</td>
<td>0.03</td>
<td>0.03</td>
<td>0.04</td>
<td>0.03</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Calverley et al. NEJM 2007
### AEs of interest which started during treatment: Rate per treatment year

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N = 1544)</th>
<th>SALM (N = 1542)</th>
<th>FP (N = 1552)</th>
<th>SFC (N = 1546)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candidiasis</td>
<td>0.02</td>
<td>0.02</td>
<td>0.09</td>
<td>0.07</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>0.004</td>
<td>0.005</td>
<td>0.017</td>
<td>0.028</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>0.113</td>
<td>0.114</td>
<td>0.102</td>
<td>0.087</td>
</tr>
</tbody>
</table>

Calverley et al. NEJM 2007
<table>
<thead>
<tr>
<th></th>
<th>Placebo (N = 1544)</th>
<th>SALM (N = 1542)</th>
<th>FP (N = 1522)</th>
<th>SFC (N = 1546)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>12.3</td>
<td>13.3</td>
<td>18.3†</td>
<td>19.6 ††</td>
</tr>
</tbody>
</table>

† p<0.001 FP vs placebo; †† p<0.001 SFC vs placebo and salmeterol

* Kaplan-Meier estimate

Calverley et al. NEJM 2007
## Probability* of having a fracture or eye disorder

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N = 1544)</th>
<th>SALM (N = 1542)</th>
<th>FP (N = 1522)</th>
<th>SFC (N = 1546)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fractures (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>5.1</td>
<td>5.1</td>
<td>5.4</td>
<td>6.3</td>
</tr>
<tr>
<td>Non-traumatic</td>
<td>1.8</td>
<td>2.5</td>
<td>1.7</td>
<td>1.7</td>
</tr>
<tr>
<td><strong>Eye disorders (%)</strong></td>
<td>3.6</td>
<td>4.3</td>
<td>4.1</td>
<td>5.2</td>
</tr>
</tbody>
</table>

All treatment comparisons are non-significant

* Kaplan-Meier estimate

Calverley et al. NEJM 2007
## Safety sub-study in USA: Bone mineral density measurements

<table>
<thead>
<tr>
<th>Week 158</th>
<th>Placebo (N = 164)</th>
<th>SAL (N = 166)</th>
<th>FP (N = 163)</th>
<th>SFC (N = 165)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMD at Hip</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>52</td>
<td>78</td>
<td>65</td>
<td>82</td>
</tr>
<tr>
<td>Adjusted % change from baseline*</td>
<td>–3.1</td>
<td>–1.7</td>
<td>–2.9</td>
<td>–3.2</td>
</tr>
<tr>
<td><strong>BMD at Lumbar Spine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>50</td>
<td>76</td>
<td>63</td>
<td>81</td>
</tr>
<tr>
<td>Adjusted % change from baseline*</td>
<td>0</td>
<td>1.5</td>
<td>–0.3</td>
<td>–0.3</td>
</tr>
</tbody>
</table>

* All treatment comparisons are non-significant

Calverley et al. NEJM 2007
## Safety sub-study in USA: Ocular assessments

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N = 164)</th>
<th>SALM (N = 166)</th>
<th>FP (N = 163)</th>
<th>SFC (N = 165)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with no cataracts present at baseline</td>
<td>47</td>
<td>41</td>
<td>47</td>
<td>52</td>
</tr>
<tr>
<td>Number of patients who developed cataracts at 3 years, n (%)</td>
<td>10/47 (21%)</td>
<td>6/41 (15%)</td>
<td>8/47 (17%)</td>
<td>14/53 (26%)</td>
</tr>
</tbody>
</table>

Calverley *et al.* NEJM 2007
Safety conclusions

- SFC was generally well tolerated over three years in patients with moderate to severe COPD

- Despite an increase in cases of pneumonia, the data suggest there was no corresponding increase in mortality with SFC due to pneumonia, although numbers are small

- There was no difference in the probability of total or non-traumatic bone fractures between groups

- There were no differences in BMD or the number of patients developing cataracts between groups

Calverley et al. NEJM 2007
TORCH: Results summary

SFC 50/500, in COPD patients with FEV₁ < 60% predicted

- Had a trend towards improved survival vs placebo
- Significantly maintains and improves health status vs placebo and components
- Significantly reduces the rate of exacerbations vs placebo and components
- Significantly improves lung function vs placebo and components
- Is generally well tolerated over 3 years with a lack of significant effect on systemic effects of steroids such as bone and eye disorders in COPD patients
- Led to increase in cases of pneumonia, but with no corresponding increase in mortality with SFC treatment

Calverley et al. NEJM 2007
TORCH: Conclusions

- COPD is the only major cause of death which is increasing in prevalence
- TORCH is the first study to demonstrate a potential survival benefit of pharmacotherapy in COPD patients
- In addition to the effect on mortality, SFC also decreased exacerbations and improved health status and lung function
- SFC was generally well tolerated over three years. There was an increase in cases of pneumonia but no corresponding increase in mortality due to pneumonia.
- These results demonstrate the clinical efficacy of SFC 50/500 µg bd in patients with FEV₁ < 60% predicted.

Calverley et al. NEJM 2007