Clinical Cardiovascular Safety Issues in COPD drug development

Industry perspective

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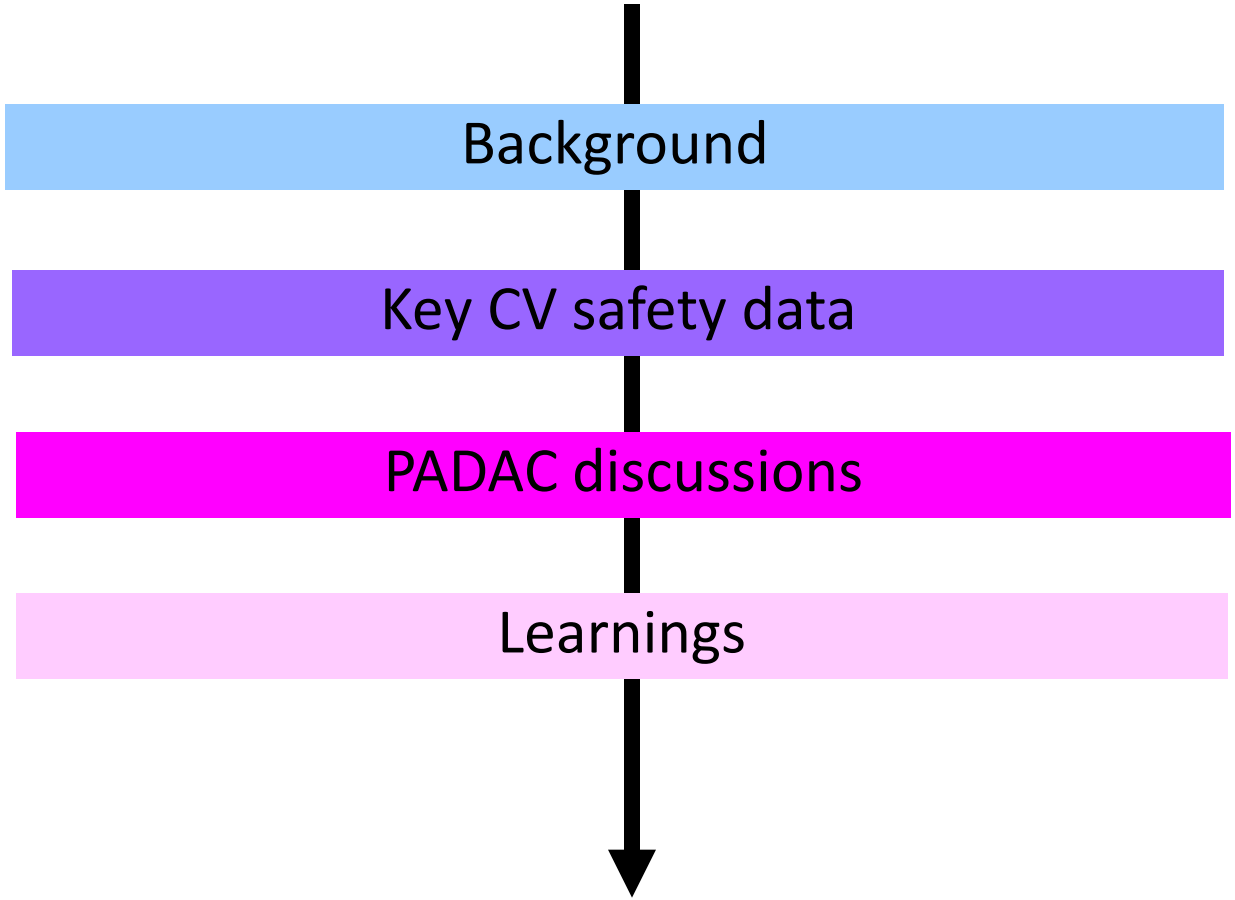
Agenda


Background
Key CV safety data
PADAC discussions
Learnings

CV disease in COPD patients

- COPD patients have high prevalence of CVD
  - CVD frequent cause of death [1]
  - Increased CV mortality with lower FEV1 [2]
  - COPD exacerbations increase risk of MI and stroke [3]
- COPD a risk factor for arrhythmias
  - High prevalence of atrial tachycardia [4]
  - Risk of higher prevalence of ventricular arrhythmias i.e. non-sustained VT [5]
- Risk of lower ejection fraction in COPD [6]

1. McGarvey LP. Thorax 2007;62:411
2. Sin DD. Proc Am Thorac Soc 2005;2:8
3. Donaldson GC. Chest 2010; 37:1091
4. Hanrahan JP. Medicine 2008;87:319
5. Yildiz P. Chest 2002;122:2055
6. Enriquez JR. Chest 2011; 140:604

Potential COPD drug-related CV risks

LABA safety

- Increase in heart rate and arrhythmias
  - Specifically atrial tachycardias
- Hospitalizations, intubations and deaths related to LABA use in asthma
  - Large prospective LABA studies currently underway
  - Signal has not been shown in patients with COPD

LAMA safety

- Increase in heart rate and arrhythmias
  - Specifically atrial tachycardias
- Increased risk of stroke, CV death and MI raised in meta-analysis [1,2]
  - UPLIFT did not show an increased risk of stroke, MI or death [3,4]
  - TIOSPIR confirmed UPLIFT results for Respimat device [5]

1. Singh S. JAMA 2008:300:1439
2. Lee TA. Annnals of Internal Medicine 2008;149:380
3. Tashkin DP. NEJM 2008:359:1543
4. Michele TM. NEJM 2010;363:1097
5. Wise RA. NEJM 2013:369:1491

BREO™ ELLIPTA™ and ANORO™ ELLIPTA™

Indications and Usage

BREO™ ELLIPTA™

- Long-term, once-daily, maintenance treatment of airflow obstruction and for reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD)
- Important limitations: Not indicated for relief of acute bronchospasm or for treatment of asthma

ANORO™ ELLIPTA™

- Long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD)
- Important limitations: Not indicated for the relief of acute bronchospasm or for the treatment of asthma

BREO™ ELLIPTA™ and ANORO™ ELLIPTA™

BREO™ ELLIPTA™

- Vilaterol (LABA) combined with fluticasone (ICS)
- PADAC meeting April 17th 2013
- Key safety aspects
  - Systemic/local ICS effects
  - LABA safety with regards to CV effects and Asthma composite endpoint
- FDA approval May 10th 2013

ANORO™ ELLIPTA™

- Vilanterol (LABA) combined with umeclidinium (LAMA)
- PADAC meeting September 10th 2013
- Key safety aspects
  - Cardiovascular safety around MACE and Cardiovascular Events of Special Interest
- FDA approval December 18th 2013

BREO™ ELLIPTA™ Cardiovascular Events* 6-month Lung Function Studies (HZC112206 and HZC112207)

	Placebo N = 412	FF/VI 50/25 N = 206	FF/VI 100/25 N = 410	FF/VI 200/25 N = 205	VI 25 N = 408	FF 100 N = 410	FF 200 N = 203
Cardiac arrhythmias	30 (7%)	11 (5%)	22 (5%)	10 (5%)	20 (5%)	23 (6%)	16 (8%)
Ischemic heart disease	4 (<1%)	3 (1%)	4 (<1%)	1 (<1%)	3 (<1%)	4 (<1%)	2 (<1%)
Cardiac failure	3 (<1%)	1 (<1%)	3 (<1%)	4 (2%)	3 (<1%)	4 (<1%)	0
Cerebrovascular disorders	0	2 (<1%)	4 (<1%)	1 (<1%)	2 (<1%)	4 (<1%)	0

* Cardiac Standardized MedDRA Queries (SMQ)

ANORO™ ELLIPTA™
Cardiovascular Adverse Events of Special Interest
Primary Efficacy Studies

Adverse Event Report Category n (%) [IR]	Placebo N=555 SY=208	UMEC/VI 62.5/25 N=842 SY=346	UMEC/VI 125/25 N=832 SY=336	UMEC 62.5 N=418 SY=168	UMEC 125 N=629 SY=249	VI 25 N=1034 SY=411	TIO N=423 SY=173
Any event	**40 (7) [192.7]**	**70 (8) [202.4]**	**55 (7) [163.6]**	**41 (10) [244.2]**	**52 (8) [208.9]**	**95 (9) [231.0]**	**27 (6) [156.0]**
Cardiac ischemia	5 (<1) [24.1]	11 (1) [31.8]	12 (1) [35.7]	7 (2) [41.7]	5 (<1) [20.1]	12 (1) [29.2]	4 (<1) [23.1]
Cardiac arrhythmias	18 (3) [86.7]	24 (3) [69.4]	19 (2) [56.5]	20 (5) [119.1]	20 (3) [80.4]	46 (4) [111.9]	9 (2) [52.0]
Hypertension	11 (2) [53.0]	25 (3) [72.3]	17 (2) [50.6]	12 (3) [71.5]	21 (3) [84.4]	29 (3) [70.5]	11 (3) [63.6]
Cardiac failure	6 (1) [28.9]	11 (1) [31.8]	11 (1) [32.7]	7 (2) [41.7]	7 (1) [28.1]	12 (1) [29.2]	5 (1) [28.9]
Stroke	2 (<1) [9.6]	1 (<1) [2.9]	1 (<1) [3.0]	1 (<1) [6.0]	1 (<1) [4.0]	3 (<1) [7.3]	1 (<1) [5.8]
Acquired long QT	0	0	2 (<1) [5.9]	1 (<1) [6.0]	0	0	0
Sudden death	0	0	0	0	0	1 (<1) [2.4]	0

ANORO™ ELLIPTA™
Cardiovascular Adverse Events of Special Interest
Long Term Safety Study

Adverse Event Report Category n (%) [IR]	Placebo N=109 SY=80	UMEC/VI 125/25 N=226 SY=177	UMEC 125 N=227 SY=167
Any event	**25 (23) [311.0]**	**34 (15) [192.6]**	**49 (22) [293.1]**
Cardiac ischemia	4 (4) [49.8]	4 (2) [22.7]	4 (2) [23.9]
Cardiac arrhythmias	17 (16) [211.5]	26 (12) [147.3]	39 (17) [233.3]
Hypertension	7 (6) [87.1]	8 (4) [45.3]	6 (3) [35.9]
Cardiac failure	1 (<1) [12.4]	2 (<1) [11.3]	4 (2) [23.9]
Stroke	0	0	1 (<1) [6.0]
Acquired long QT	0	0	0
Sudden death	0	0	0

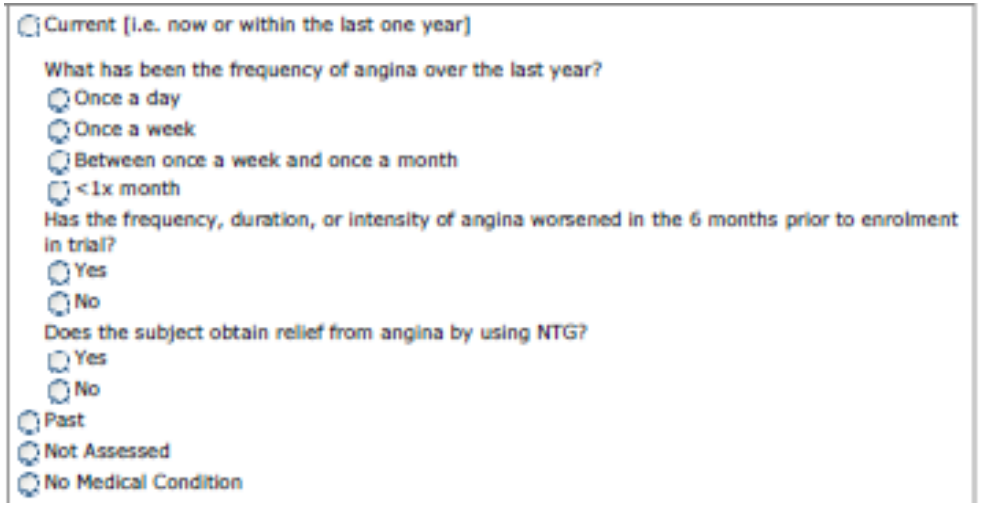
Discussion at ANORO™ ELLIPTA™ Adcom

- Discussion around numeric imbalances of ischemic events and supraventricular arrhythmias
- Cardiac exclusion criteria (e.g. 28 ECG exclusions)
  - ECG exclusions not widely reflective of post launch clinical practice
  - Potentially resulted in a low cardiac event rate – i.e. selection bias towards “healthier” population, therefore…
- Can phase III results be generalized to typical COPD population?
- Discussion regarding patient withdrawals for cardiac reasons
  - Would have appreciated more detail from subjects who were discontinued for cardiac reasons and what happened during follow-up

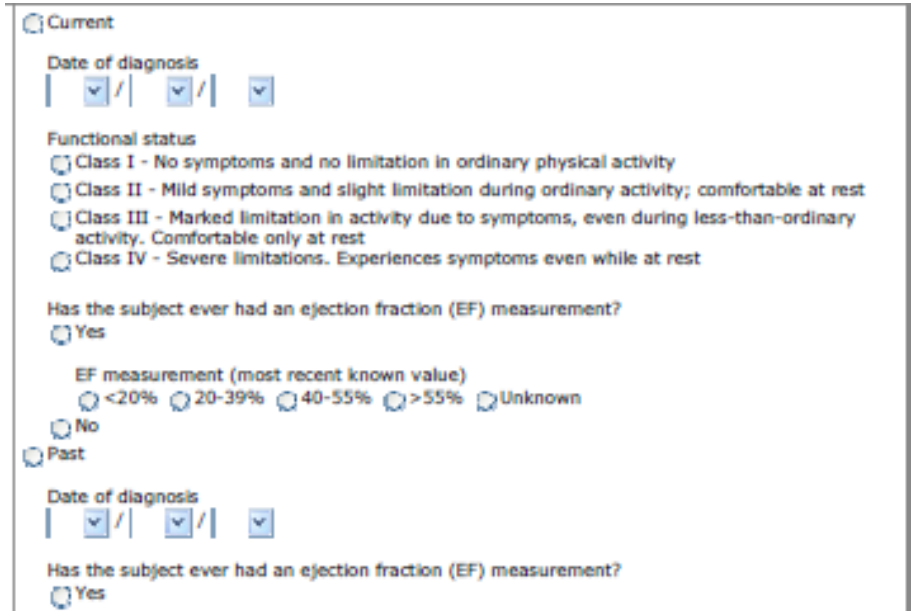
Improvements for future COPD development programs
Before start / at baseline

- Consider what is essential in terms of exclusion/discontinuation criteria
  - Ensure as close to real world patient profile as feasible in clinical trials
- Improved collection of baseline cardiovascular information
  - Updated medical history eCRF with additional questions concerning important CV conditions e.g angina pectoris, congestive heart failure

Angina pectoris



Congestive heart failure



Improvements for future COPD development programs
During study and after stopping study drug

- CV eCRF forms:
  - Enable collection of detailed information on all major CV events at time of event (i.e. death, MI, CHF…)
- Better collection of information regarding patient withdrawals
  - E.g. need for telephone follow-up, targeted f/u questions, etc
  - Will help to determine if patients are dropping out of a study for a specific cardiac event or just a random assortment of CV events
- CV Adjudication:
  - GSK is currently setting up a defined CV event adjudication group to assist teams in a streamlined fashion

Summary

- BREO™ ELLIPTA™ and ANORO™ ELLIPTA™ provided meaningful insights into CV safety issues associated with COPD drug development
- Key questions discussed were
  - Impact of CV exclusion criteria
  - Importance of CV data collection at baseline, during the study as well as at the end of the treatment period
- Key learnings are currently being applied and further explored
  - Aim for broad patient population that reflects subjects who will use the drug after approval
  - Enhanced and facilitated collection of CV data during clinical studies