Anoro Ellipta Case Study: Characterizing and Communicating Uncertainty in the Assessment of Benefit/Risk

IOM Workshop
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Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

Outline

- Description of the product
- Safety concerns with long-acting muscarinic antagonists
- Clinical safety data for Anoro Ellipta
- Advisory Committee recommendations/GSK's proposal
- FDA's decision
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Anoro Ellipta (UMEC/VI) Product Information

Source: NDA 203-975 Briefing Document, pg. 50 (Figure 9)

Umeclidinium (UMEC) and Vilanterol (VI) delivered by Ellipta device

- UMEC: long-acting muscarinic antagonist (LAMA)
- VI: long-acting beta-agonists (LABA)
- Approved on December 18, 2013
- Indicated for long-term, maintenance bronchodilator treatment of Chronic Obstructive Pulmonary Disease
- 1 inhalation (UMEC/VI 62.5 mcg/25 mcg) once daily

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LAMAs: Cardiovascular Events and Stroke

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- Stroke signal identified in 29 pooled trials with tiotropium
- Numerical imbalance in all-cause mortality noted for Spiriva Respimat vs. placebo in 3 trials

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- Meta-analysis[1] and case-controlled[2] analyses suggesting increased risk of mortality, stroke, and/or cardiovascular events, published

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  --5992 patients, 4 years
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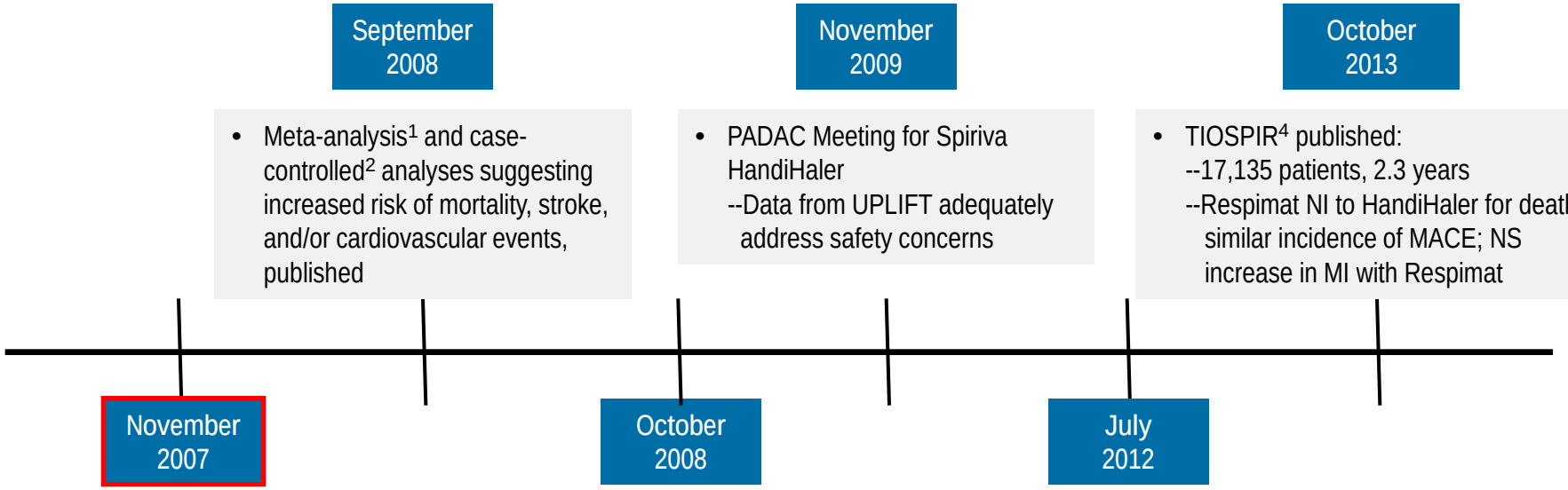
LAMAs: Cardiovascular Events and Stroke



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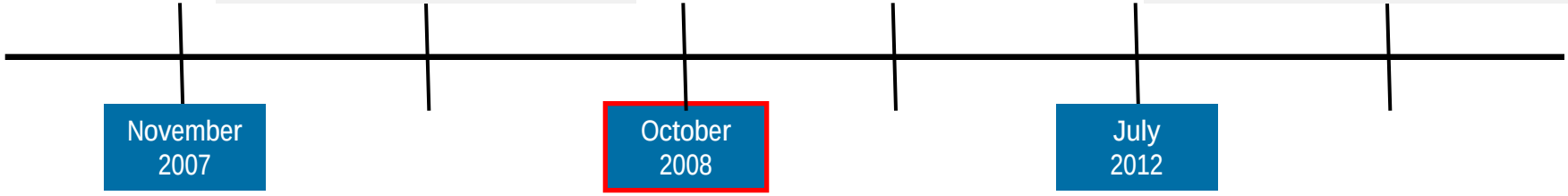

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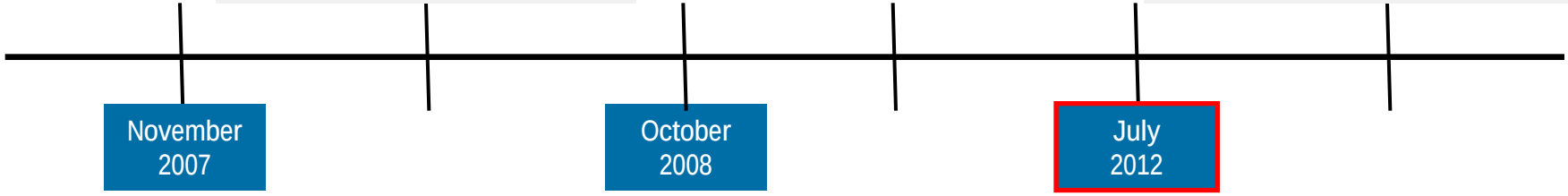

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Extent of Exposure

"All COPD Clinical Studies" Grouping of Trials:

Primary Efficacy, Long-Term Safety, and 9 Additional Trials

Summary of Exposure, "All COPD Clinical Studies"

	Placebo N=1637	UMEC/VI 62.5/25 N=1124	UMEC/VI 125/25 N=1330	UMEC 62.5 N=576	UMEC 125 N=1087	VI 25 N=2501	TIO N=423
Range, n(%)							
> 4 weeks	1366 (83)	1066 (95)	1262 (95)	548 (95)	954 (88)	2296 (92)	395 (93)
> 8 weeks	1251 (76)	1034 (92)	1212 (91)	522 (91)	900 (83)	2153 (86)	382 (90)
> 12 weeks	1103 (67)	932 (83)	1129 (85)	450 (78)	827 (76)	2045 (82)	374 (88)
> 24 weeks	394 (24)	326 (29)	462 (35)	154 (27)	370 (34)	1147 (46)	116 (27)
> 36 weeks	73 (4)	0	160 (12)	0	154 (14)	622 (25)	0
> 48 weeks	66 (4)	0	146 (11)	0	133 (12)	590 (24)	0
> 52 weeks	19 (1)	0	37 (3)	0	35 (3)	209 (8)	0

Source: NDA 203-975, Section 5.3.5.3. (ISS), pg. 70 (Table 14)
Key: N=ITT Population

Extent of Exposure

Primary Efficacy and Long-Term Safety Trial

Summary of Exposure, Primary Efficacy and Long-Term Safety Trials, N							
	Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	TIO
Primary Efficacy	555	842	832	418	629	1034	423
Long-Term Safety	109	--	226	--	227	--	--

Source: NDA 203-975, Section 5.3.5.3. (ISS), pg. 64 (Table 9)
Key: N=ITT Population

Deaths

Summary of Deaths, Primary Efficacy and Long-Term Safety Trials

	Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	TIO
	N	N	N	N	N	N	N
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Primary Efficacy Trials	555	842	832	418	629	1034	423
	2* (0.4)	5 (0.6)	1 (0.1)	3 (0.7)	2 (0.3)	6 (0.6)	2 (0.5)
Long-Term Safety Trial	109	--	226	--	227	--	--
	1 (0.9)	--	0	--	4 (2)	--	--

*A post-treatment death reported after trial closure for a patient in the placebo group of Trial DB2113373 is not included in this count
Source: NDA 203-975, Section 5.3.5.3. (ISS), pg. 64 (Table 9), pg. 150 (Table 86)
Key: N=ITT Population

Nonfatal Serious Adverse Events

Summary of Nonfatal Serious Adverse Events*, Primary Efficacy and Long-Term Safety Trials

	Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	TIO
	N	N	N	N	N	N	N
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Primary Efficacy Trials	555	842	832	418	629	1034	423
	24 (4)	47 (6)	43 (5)	27 (6)	35 (6)	54 (5)	20 (5)
Long-Term Safety Trial	109	--	226	--	227	--	--
	7 (6)	--	14 (6)	--	15 (7)	--	--

*Serious Adverse Drug Experience is defined in 21 CFR 312.32 as any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect

Source: NDA 203-975 (April 26, 2013 submission), Section 1.11.3 (Efficacy Information Amendment), pg. 6 (Table 4), pg. 11 (Table 5)

Key: N=ITT Population

Cardiovascular Risk

- Major Adverse Cardiac Events (MACE)
  - Ischemia/Infarction
  - Stroke
  - Cardiovascular Death

- Cardiovascular Adverse Events of Special Interest (AESI)
  - Acquired Long QT
  - Cardiac Arrhythmia
  - Cardiac Failure
  - Cardiac Ischemia
  - Hypertension
  - Sudden Death
  - Stroke

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Cardiovascular AESI

Serious Cardiovascular AESIs, by Trial Grouping

	Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	TIO
	N (SY)						
	Number of Subjects (Number of Subjects per 1000 SY)						
Primary Efficacy	555 (208)	842 (346)	832 (336)	418 (168)	629 (249)	1034 (411)	423 (173)
	2 (10)	8 (23)	7 (21)	7 (42)	9 (36)	18 (44)	3 (17)
Long-Term Safety	109 (80)	--	226 (177)	--	227 (167)	--	--
	2 (25)	--	4 (23)	--	5 (30)	--	--

Source: NDA 203-975, Section 5.3.5.3. (ISS), pg. 210 (Table 119), pg. 212 (Table 120), pg. 221 (Table 126); pg. 222 (Table 127)
Key: N=ITT Population; SY=subject-years

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Serious Cardiovascular AESIs, by Trial Grouping

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Cardiovascular AESI

Serious Cardiovascular AESI, Cardiac Ischemia Subgroup, by Preferred Term, Primary Efficacy Trials

	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
	Number of Subjects (Number of Subjects per 1000 SY)						
Any term	1 (5)	6 (17)	3 (9)	4 (24)	3 (12)	6 (15)	1 (6)
Acute MI	0	0	0	0	1 (4)	3 (7)	0
Angina pectoris	1 (5)	0	0	0	0	1 (2)	0
Angina unstable	0	1 (3)	0	1 (6)	1 (4)	0	0
↑ Cardiac enzymes	0	0	0	0	0	1 (2)	0
CAD	0	0	2 (6)	2 (12)	0	1 (2)	0
ECG TWI	0	1 (3)	0	0	0	0	0
MI	0	3 (9)	1 (3)	0	1 (4)	0	0
Myocardial ischemia	0	1 (3)	0	0	0	0	0
Troponin increased	0	0	0	1 (6)	0	0	0
Vascular graft occ.	0	0	0	0	0	0	1 (6)

Source: NDA 203-975, Section 5.3.5.3. (ISS), pg. 211 (Table 119), pg. 212-213 (Table 120); Key: CAD=coronary artery disease; MI=myocardial infarction; Occ=occlusion

Cardiovascular AESI

Serious Cardiovascular AESI, Cardiac Ischemia Subgroup, by Preferred Term, Primary Efficacy Trials

	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
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Any term	1 (5)	6 (17)	3 (9)	4 (24)	3 (12)	6 (15)	1 (6)
Acute MI	0	0	0	0	1 (4)	3 (7)	0
Angina pectoris	1 (5)	0	0	0	0	1 (2)	0
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ECG TWI	0	1 (3)	0	0	0	0	0
MI	0	3 (9)	1 (3)	0	1 (4)	0	0
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Troponin increased	0	0	0	1 (6)	0	0	0
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Source: NDA 203-975, Section 5.3.5.3. (ISS), pg. 211 (Table 119), pg. 212-213 (Table 120); Key: CAD=coronary artery disease; MI=myocardial infarction; Occ=occlusion

Cardiovascular AESI

Serious Cardiovascular AESI, by Subgroup, Long-Term Safety Trial			
	Placebo N=109 SY=80	UMEC/VI 125/25 N=226 SY=177	UMEC 125 N=227 SY=167
	Number of Subjects (Number of Subjects per 1000 SY)		
Acquired long QT	0	0	0
Arrhythmias	0	0	1 (6)
Cardiac failure	1 (12)	1 (6)	2 (12)
Ischemia	2 (25)	3 (17)	2 (12)
Hypertension	0	1 (6)	1 (6)
Sudden death	0	0	0
Stroke	0	0	1 (6)

Source: NDA 203-975, Section 5.3.5.3 (ISS), pg. 221 (Table 126), pg. 222 (Table 127)
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Cardiovascular Risk, Summary

Event	Umeclidinium	Umeclidinium/Vilanterol
	compared to placebo	compared to placebo
MACE (narrow)	0.8 (0.3, 2.2)	0.6 (0.2, 1.6)
CVD SAE	1.3 (0.6, 3.0)	1.0 (0.4, 2.3)

Source: Greg Levin, Ph.D., FDA statistical reviewer
Note: Cell contents are hazard ratio (95% confidence interval) from proportional hazards models
UMEC doses of 62.5 and 125, and UMEC/VI doses of 62.5/25 and 125/25 are pooled

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Cardiovascular Risk, Summary

- Evaluation of cardiovascular risk included MACE and cardiovascular AESI analyses
- Imbalances demonstrated for events related to ischemia
- Considerations
  - Cardiovascular AESI imbalances seen in primary efficacy trials are not also observed in long-term safety trial
    - Impact of missing data
  - Overall number of events is low

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Advisory Committee Recommendations

- Committee makes non-binding recommendations to FDA that inform the Agency's decision-making
- September 10, 2013 meeting of the Pulmonary-Allergy Drugs Advisory Committee discussed UMEC/VI
- Response to question on adequacy of the safety data:
  - 10 yes, 3 no, 0 abstain
- Both assenting and dissenting members raised concern about the generalizability of the safety data; some recommended obtaining additional data

GSK's Proposal for Further Evaluation

- Applicant proposed observational studies to explore any possible cardiovascular risks

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FDA's Decision

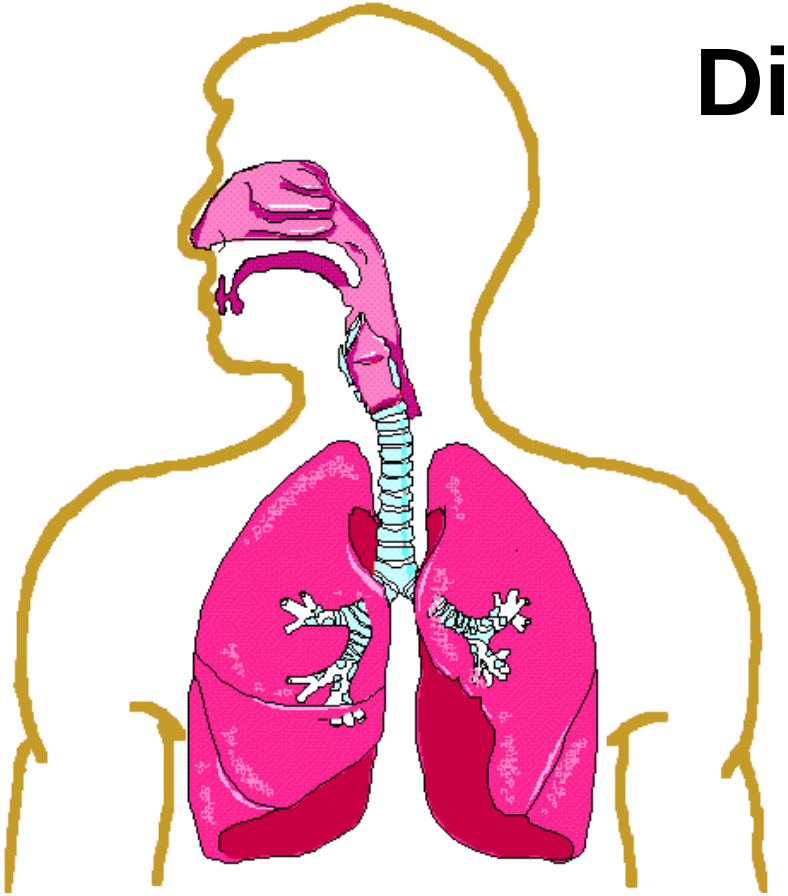
- Anoro Ellipta approved on December 18, 2013
- FDA concluded that there was substantial evidence of efficacy and safety, with a positive benefit-risk ratio
- Approval Letter did not require any post-marketing trials

"…contemplation must occur regarding at what point CV outcome trials should no longer be required of LAMA agents. I believe we are at that point. As previously noted, we have not reviewed TIOSPIR yet, and if we come to a different conclusion from the published results, then we may need to revisit this conclusion."

Source: (Dr. Curtis Rosebraugh, Office Director Memo, pg. 13-14; available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203975Orig1s000ODMemo.pdf; accessed February 7, 2014)

Summary

- Numerical imbalances in cardiovascular serious adverse events are observed in the UMEC/VI data, but the overall number of events was low
- Historically, there has been concern about the cardiovascular safety profile of LAMAs, but the results from large RCTs have generally been reassuring
- FDA concluded that the benefit/risk of UMEC/VI is positive, and a postmarketing safety trial is not required



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