Cardiovascular Events of Japanese patients with COPD in clinical trials

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This presentation is based on publicly-available data/information for the drug at this time.

Approved Inhalation drugs for COPD in Japan as of February 28th, 2014

class	drug	product name	inhaler (μg)	date of approval
LAMA/LABA	Indacaterol/ Glycopyrronium	Ultibro	110/50(DPI)	2013/11
LAMA	Glycopyrronium	Seebri	50 (DPI)	2012/11
LABA	Formoterol	Oxis	9 (DPI)	2013/09
LAMA	Indacaterol	Onbrez	150 (DPI)	2011/09
LAMA	Tiotropium	Spiriva	18(DPI); 5(SMI)	2010/05
ICS/LABA	Formoterol/ Budesonide	Symbicort	4.5/160 (DPI)	2010/01
ICS/LABA	Salmeterol/ Fluticasone	Advair/Adoair	50/250 DPI ; 25/125MDI	2009/01
LABA	Salmeterol	Serebent	25-50 (DPI)	2002/06

Recent trials in JAPAN 1
Indacaterol/Glycopyrronium *Ultibro*-1

- Pivotal trial (A2303) including Japanese patients
  - placebo- and active-controlled design

	Indacaterol /glycopyrronium	Indacaterol	Glyco-pyrronium	Tiotropium	Placebo	Total
global	474	476	473	480	232	2135
Japanese	40	39	36	37	15	167

  - Patients background

	age (ave.)	age≧65	male	BMI	current smoking
global	64 y.o.	48.6 %	75.4 %	25.9 kg/m^2	39.7 %
Japanese	69 y.o.	80.0 %	96.2 %	22.7 kg/m^2	23.6 %

Characteristics of Japanese COPD patients are older age, male-dominant and lower-weight.

Recent trials in JAPAN 1
Indacaterol/Glycopyrronium *Ultibro*-2

- Japan domestic long term trial (6 months)

	Indacaterol/glycopyrronium	Tiotropium
Severe CCV events	3/119 (2.5%)	0/39
MACE*	3/119 (2.5%)	0/39

*MACE ;major adverse cardiovascular events (Non fatal angina, coronary bypass, non fatal MI, non fatal stroke and hospitalized cardiac failure)

- Total sum of global 4 trials (6 months)

	Indacaterol/ glycopyrronium	Indacaterol	Glyco-pyrronium	Tiotropium	Fluticasone /Salmeterol	Placebo
Severe CCV events	6/1076 (0.6%)	6/476 (1.3%)	7/473 (1.5%)	4/519 (0.8%)	3/264 (1.1%)	1/345 (0.3%)
MACE	4/1076 (0.4%)	4/476 (0.8%)	6/473 (1.3%)	3/519 (0.6%)	3/264 (1.1%)	1/345 (0.3%)

There is not so much difference between Japanese and global population in frequency of CCV events and MACE.

Recent trials in JAPAN 2
Formoterol/Budesonide *Symbicort-1*

- Pivotal trial (D589DC00007) including Japanese patients

	Formoterol /Budesonide	Formoterol	Total
Global	636	657	1293
Japanese	147	165	312

- Patients background

	age≧65	Smoking (≧40 pack year)
Global	44.8 %	46.3%
Japanese	78.2 %	78.8%

Characteristics of Japanese COPD patients are older age and heavy smoking.

Recent trials in JAPAN 2
Formoterol/Budesonide *Symbicort-2*

- CCV events in long term trials

	Japan domestic long term trials (6 months) (D589DC00008)		Global long term 4 trials (over 6 months)	
	Formoterol/ Budesonide	standard therapy	Formoterol/ Budesonide	placebo
age < 65	3/30 (10%)	1/23 (4.3%)	49/1056 (4.6%)	26/645 (4.0%)
65≦age	7/100 (7%)	8/107 (7.4%)	94/952 (9.9%)	38/597 (6.3%)

Concerning long term trials, there is not so much difference between Japanese and global population in frequency of CCV events .

At the present time,

- There is not so much difference between Japanese and global population in frequency of CCV events according to the publicly-available data.

Japanese Drug Package Insert -1 “Important Precautions”

“Continuous excessive use of Symbicort/Ultibro may induce arrhythmia, or even cardiac arrest in some cases.

Symbicort/Ultibro should not be administered at doses above the recommended dose regimen.”

Japanese Drug Package Insert -2 “Adverse Reactions”

1) Clinically significant adverse reactions

(none of cardiovascular)

2) Other adverse reactions

Cardiovascular; (<1%) Palpitation, arrhythmia, tachycardia, angina, and hypertension.

The points to observe drug use of Japanese COPD patients in the future

- Data of several clinical trials shows that characteristics of Japanese COPD patients are older age, male-dominant and heavy smoking compared to global population.
- Most severe COPD patients with...
  - Taking Continuous Oxygen Therapy (HOT)
  - Having history of COPD exacerbation within 4weeks

  were excluded from the clinical trials by criteria.
- Since more severe, and older patients will have higher risks of cardiovascular complication, more careful observation will be necessary for post marketing surveillance.