Cost-Utility Analysis of Apremilast for the Treatment of Moderate to Severe Psoriasis in Spain

J. Manuel Carrascosa, MD[1]; Francisco Vanaclocha, PhD[2]; Teresa Caloto, PhD, MPH[3]; María Echave, MSc[4]; Itziar Oyagüez, MSc[4]; Tom Tencer, PhD[5]

[1]Department of Dermatology, Germans Trias i Pujol University Hospital, Barcelona, Spain; [2]Department of Dermatology, University Hospital, Madrid, Spain; [3]Department of Health Economics, Celgene Corporation, Madrid, Spain; [4]Pharmacoeconomics & Outcomes Research Iberia, Madrid, Spain; [5]Celgene Corporation, Warren, NJ, USA

BACKGROUND

- Psoriasis is an immune-mediated inflammatory disease that may have a major impact on quality of life, especially in patients with moderate to severe disease.[1]
- Psoriasis is characterised by a rapid buildup of the cells on the surface of the skin (epidermis), which results in thick, silvery, dry scales that are itchy and painful.[2]
- There is evidence of a delay in using systemic agents and biologicals in patients with moderate to severe psoriasis; this delay exceeds 3 years in 50% of patients.[3]
- Conventional systemic agents for psoriasis include cyclosporine and methotrexate or psoralen plus ultraviolet A light (PUVA). Biological therapies are used when response to previous conventional systemic therapies or PUVA therapy is inadequate.[4]
- Apremilast is an orally administered, small-molecule phosphodiesterase 4 inhibitor. It has a novel mechanism of action, targeting multiple steps in the pathogenesis of psoriasis. The marketing authorisation from the European Medicines Agency for the use of apremilast in patients with psoriasis and psoriatic arthritis was granted on January 15, 2015.

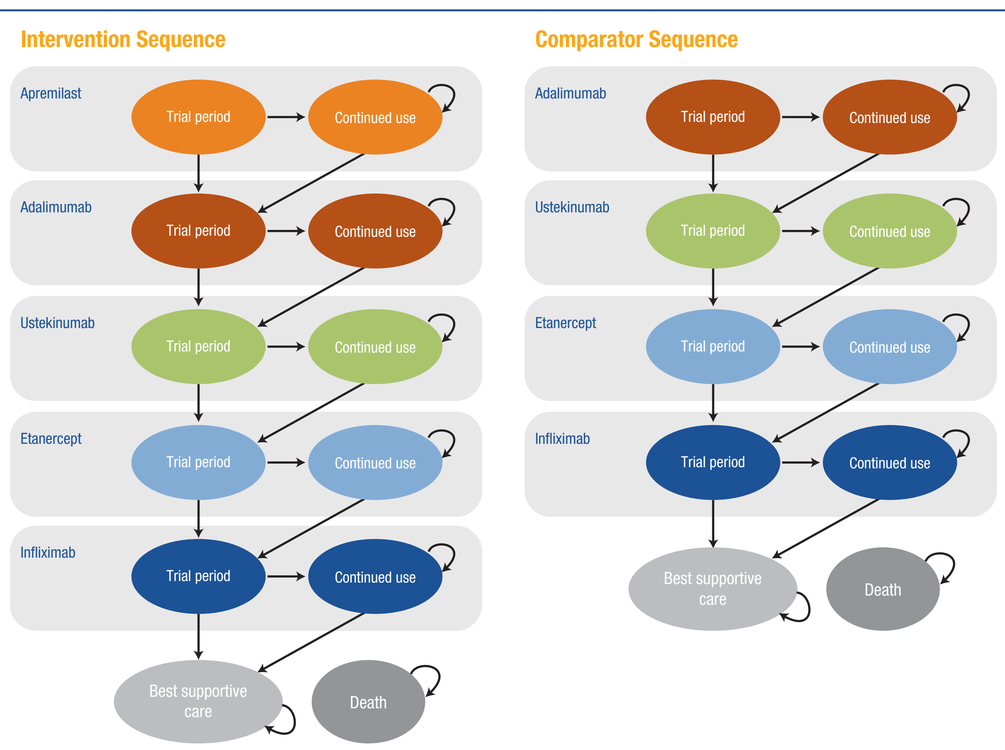
OBJECTIVE

- This cost-utility model was developed from the payer perspective to assess the impact of placing apremilast before biologicals for the treatment of moderate to severe plaque psoriasis in patients in Spain who have failed to respond to, are intolerant of, or have a contraindication to previous systemic treatment.

METHODS

- A 20-year Markov model with monthly cycle duration was developed (**Figure 1**).
- Any-cause mortality rates in the Spanish general population were included in order to estimate quality-adjusted life-years (QALYs).
- Treatment strategies consisted of an apremilast before biologicals sequence compared with a biologicals-only sequence.
- Sequential biologicals, based on Spanish clinical practice, were adalimumab, ustekinumab, etanercept, and infliximab for both strategies. Patients who failed infliximab were assumed to receive best supportive care (BSC).

Figure 1. Markov Model Structure



- A ≥75% reduction in Psoriasis Area and Severity Index (PASI-75) was used as the efficacy measure. PASI-75 response rates for each drug were derived from a meta-analysis: apremilast (29.74%), adalimumab (62.25%), ustekinumab (76.30%), etanercept (45.33%), and infliximab (85.16%). All-cause overall mortality was considered.
- Resource consumption was estimated by an expert panel, and biological doses were taken from the summaries of product characteristics. According to the Spanish National Health System (NHS) perspective, the following costs were included:
  - Drug acquisition (ex-factory price[5] with mandatory deduction[6])
    - Mean weight from patients included in apremilast pivotal clinical trials was considered to estimate drug consumption of infliximab
  - Administration (for parenteral drugs)
  - Monitoring costs
  - Unit costs (€, 2014), obtained from national databases[7] (**Table 1**)
- The price of apremilast is that submitted to the Spanish Ministry of Health for the price and reimbursement process (€820.00).

Table 1. Unit Costs (€, 2014)

Drug	Ex-factory Price[5]
Apremilast (Otezla®) 30 mg, 56 tablets – oral	€820.00*
Adalimumab (Humira®) 40 mg, 2 injections 0.8 mL – SC	€1,028.29
Etanercept (Enbrel®) 50 mg, 4 injections 1 mL – SC	€947.22
Infliximab (Remsima®) 100 mg, 1 vial – IV	€439.75
Ustekinumab (Stelara®) 45 mg, 1 injection 0.5 mL – SC	€2,747.36
Administration for parenteral drugs	**Unit cost[7]**
Drug perfusion (0.5 hour–2 hours)	€156.10
Nurse personnel	€20.87/hour
Dermatologist	€27.16/hour
Monitoring (detailed consumption provided by an expert panel)	**Annual cost**
For apremilast	€115.40
For adalimumab and etanercept	€233.30
For infliximab	€281.81
For ustekinumab	€213.53

*Apremilast price submitted to the Spanish Ministry of Health for price and reimbursement process.
IV=intravenous; SC=subcutaneous.

- An annual discount rate of 3% was applied for both costs and health benefits.[8]
- Utilities were estimated from PASI response using a previously published regression equation.[9]
- One-way deterministic and probabilistic sensitivity analyses (SA) were performed to test the robustness of the model.

RESULTS

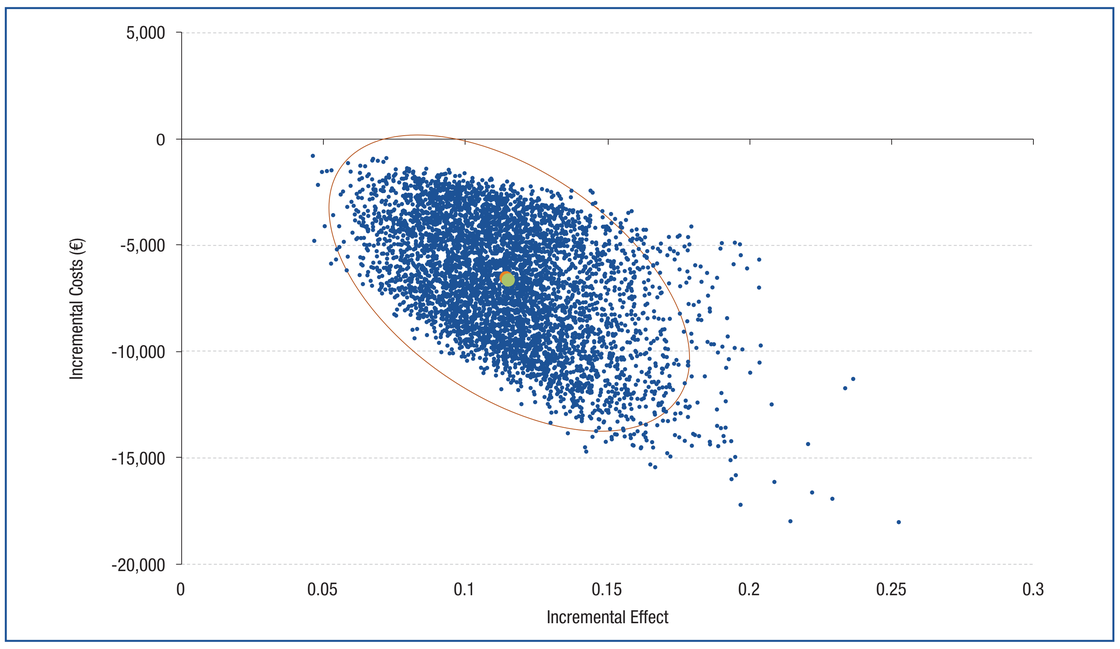
- The administration of apremilast before a sequence of biologicals was estimated to provide an additional 0.12 QALYs: 12.37 QALYs vs. 12.25 QALYs for a sequence of biologicals only.
- In the base-case assumptions, the sequence with apremilast yielded lower total costs than the sequence with biologicals only (€217,814 vs. €224,359). Under base-case assumptions, placing apremilast before biologicals is a dominant treatment strategy.
- Results of one-way deterministic SA confirm the robustness of the model: the sequence that included apremilast demonstrated higher effectiveness and lower total costs than the sequence with biologicals only in all analyses (**Table 2**).
- In the probabilistic SA, the administration of apremilast before biologicals was dominant in 100% of the simulations (**Figure 2**).

Table 2. One-Way Deterministic Sensitivity Analysis Results

Parameter	Base Case Parameters	Sensitivity Analysis Parameters	Incremental Total Cost (€)	Incremental QALY	ICER (€/QALY)
Base case ICER			-6,545	0.12	Dominant
Time horizon	20 years	10 years	-4,326	0.03	Dominant
		Lifetime (40 years)	-7,372	0.15	Dominant
Discount rate	3%	0%	-8,189	0.17	Dominant
		5%	-5,743	0.09	Dominant
Drug order in biologicals sequence	A >U >E > I	U >A >E >I	-6,595	0.11	Dominant
		E >U >A >I	-6,539	0.11	Dominant
Mean weight of patients	92.63 kg	75 kg	-5,911	0.11	Dominant
Best supportive care cost	€1,358.91	€716.53	0	0.11	Dominant
		€1,562.75	-8,622	0.11	Dominant
Hospitalization from non-responder patients	10 days/year	5 days	-7,336	0.11	Dominant
		15 days	-5,756	0.11	Dominant
Infliximab cost	€406.77	€496.06 (Remicade®)	-7,242	0.11	Dominant

A=adalimumab; E=etanercept; ICER=incremental cost-effectiveness ratio; U=ustekinumab.

Figure 2. Cost-Effectiveness Plane



LIMITATIONS

- Response rates for each treatment within the model were assessed at different time points, and no studies including all current therapies were performed. The model assumes that efficacy is maintained over a long time horizon.
- Due to the lack of studies, utilities have been considered from studies conducted in countries other than Spain. However, based on the experience and knowledge of the experts consulted, this information could also be representative of the Spanish population.
- The present model was developed from a third-party payer perspective; thus it did not include indirect costs that could be useful for a societal analysis.

CONCLUSION

- The administration of apremilast before biologicals resulted in a dominant strategy for the Spanish NHS in the treatment of patients with moderate to severe plaque psoriasis.

REFERENCES

1. Girolomoni G, Griffiths CE, Krueger J, et al. Early intervention in psoriasis and immune-mediated inflammatory diseases: a hypothesis paper. *J Dermatolog Treat.* 2015;26:103-q12.
2. Mayo Foundation for Medical Education and Research. Psoriasis. Available at: http://www.mayoclinic.com/health/psoriasis/DS00193. Accessed October 2015.
3. Maza A, Richard MA, Aubin F, et al. Significant delay in the introduction of systemic treatment of moderate to severe psoriasis: a prospective multicentre observational study in outpatients from hospital dermatology departments in France. *Br J Dermatol.* 2012;167:643–648.
4. European Medicines Agency. EPAR summary for the public. Otezla (apremilast). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/003746/WC500182630.pdf. Accessed September 2015.
5. BOT Plus Web site. Available at: http://www.portalfarma.com. Accessed September 2015.
6. Royal Decree-Law 8/2010. Available at: http://www.boe.es/boe/dias/2010/05/24/pdfs/BOE-A-2010-8228.pdf. Accessed September 2015.
7. eSalud - Información económica del sector sanitario. Available at: http://www.oblikue.com/bddcostes. Accessed September 2015.
8. Lopez-Bastida J, Oliva J, Antonanzas F, et al. Spanish recommendations on economic evaluation of health technologies. *Eur J Health Econ.* 2010;11:513-520.
9. Woolacott N, Hawkins N, Mason A, et al. Etanercept and efalizumab for the treatment of psoriasis: a systematic review. *Health Technol Assess.* 2006;10:1-233; i-iv.

This study was sponsored by Celgene Corporation.

Presented at: the ISPOR 18th Annual European Congress; 7–11 November 2015; Milan, Italy.

Cost-Utility Analysis of Apremilast for the Treatment of Moderate to Severe Psoriasis in Spain

J. Manuel Carrascosa, MD[1]; Francisco Vanaclocha, PhD[2]; Teresa Caloto, PhD, MPH[3]; María Echave, MSc[4]; Itziar Oyagüez, MSc[4]; Tom Tencer, PhD[5]

[1]Department of Dermatology, Germans Trias i Pujol University Hospital, Barcelona, Spain; [2]Department of Dermatology, University Hospital, Madrid, Spain; [3]Department of Health Economics, Celgene Corporation, Madrid, Spain; [4]Pharmacoeconomics & Outcomes Research Iberia, Madrid, Spain; [5]Celgene Corporation, Warren, NJ, USA

BACKGROUND

- Psoriasis is an immune-mediated inflammatory disease that may have a major impact on quality of life, especially in patients with moderate to severe disease.[1]
- Psoriasis is characterised by a rapid buildup of the cells on the surface of the skin (epidermis), which results in thick, silvery, dry scales that are itchy and painful.[2]
- There is evidence of a delay in using systemic agents and biologicals in patients with moderate to severe psoriasis; this delay exceeds 3 years in 50% of patients.[3]
- Conventional systemic agents for psoriasis include cyclosporine and methotrexate or psoralen plus ultraviolet A light (PUVA). Biological therapies are used when response to previous conventional systemic therapies or PUVA therapy is inadequate.[4]
- Apremilast is an orally administered, small-molecule phosphodiesterase 4 inhibitor. It has a novel mechanism of action, targeting multiple steps in the pathogenesis of psoriasis. The marketing authorisation from the European Medicines Agency for the use of apremilast in patients with psoriasis and psoriatic arthritis was granted on January 15, 2015.

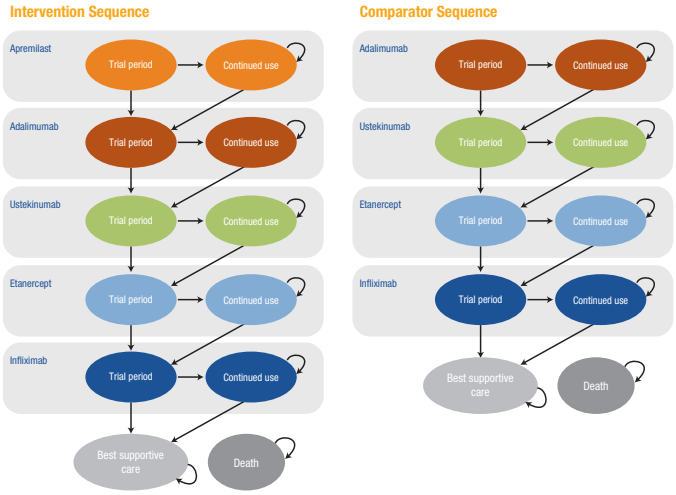
OBJECTIVE

- This cost-utility model was developed from the payer perspective to assess the impact of placing apremilast before biologicals for the treatment of moderate to severe plaque psoriasis in patients in Spain who have failed to respond to, are intolerant of, or have a contraindication to previous systemic treatment.

METHODS

- A 20-year Markov model with monthly cycle duration was developed (**Figure 1**).
- Any-cause mortality rates in the Spanish general population were included in order to estimate quality-adjusted life-years (QALYs).
- Treatment strategies consisted of an apremilast before biologicals sequence compared with a biologicals-only sequence.
- Sequential biologicals, based on Spanish clinical practice, were adalimumab, ustekinumab, etanercept, and infliximab for both strategies. Patients who failed infliximab were assumed to receive best supportive care (BSC).

Figure 1. Markov Model Structure



- A ≥75% reduction in Psoriasis Area and Severity Index (PASI-75) was used as the efficacy measure. PASI-75 response rates for each drug were derived from a meta-analysis: apremilast (29.74%), adalimumab (62.25%), ustekinumab (76.30%), etanercept (45.33%), and infliximab (85.16%). All-cause overall mortality was considered.
- Resource consumption was estimated by an expert panel, and biological doses were taken from the summaries of product characteristics. According to the Spanish National Health System (NHS) perspective, the following costs were included:
  - Drug acquisition (ex-factory price[5] with mandatory deduction[6])
    - Mean weight from patients included in apremilast pivotal clinical trials was considered to estimate drug consumption of infliximab
  - Administration (for parenteral drugs)
  - Monitoring costs
  - Unit costs (€, 2014), obtained from national databases[7] (**Table 1**)
- The price of apremilast is that submitted to the Spanish Ministry of Health for the price and reimbursement process (€820.00).

Table 1. Unit Costs (€, 2014)

Drug	Ex-factory Price[5]
Apremilast (Otezla®) 30 mg, 56 tablets – oral	€820.00*
Adalimumab (Humira®) 40 mg, 2 injections 0.8 mL – SC	€1,028.29
Etanercept (Enbrel®) 50 mg, 4 injections 1 mL – SC	€947.22
Infliximab (Remsima®) 100 mg, 1 vial – IV	€439.75
Ustekinumab (Stelara®) 45 mg, 1 injection 0.5 mL – SC	€2,747.36
Administration for parenteral drugs	**Unit cost[7]**
Drug perfusion (0.5 hour–2 hours)	€156.10
Nurse personnel	€20.87/hour
Dermatologist	€27.16/hour
Monitoring (detailed consumption provided by an expert panel)	**Annual cost**
For apremilast	€115.40
For adalimumab and etanercept	€233.30
For infliximab	€281.81
For ustekinumab	€213.53

*Apremilast price submitted to the Spanish Ministry of Health for price and reimbursement process.
IV=intravenous; SC=subcutaneous.

- An annual discount rate of 3% was applied for both costs and health benefits.[8]
- Utilities were estimated from PASI response using a previously published regression equation.[9]
- One-way deterministic and probabilistic sensitivity analyses (SA) were performed to test the robustness of the model.

RESULTS

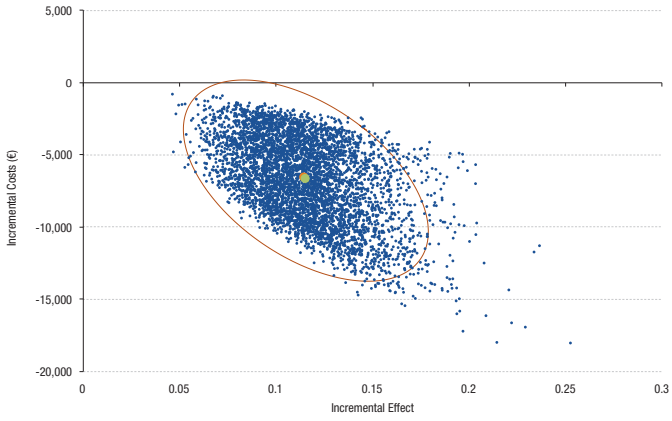
- The administration of apremilast before a sequence of biologicals was estimated to provide an additional 0.12 QALYs: 12.37 QALYs vs. 12.25 QALYs for a sequence of biologicals only.
- In the base-case assumptions, the sequence with apremilast yielded lower total costs than the sequence with biologicals only (€217,814 vs. €224,359). Under base-case assumptions, placing apremilast before biologicals is a dominant treatment strategy.
- Results of one-way deterministic SA confirm the robustness of the model: the sequence that included apremilast demonstrated higher effectiveness and lower total costs than the sequence with biologicals only in all analyses (**Table 2**).
- In the probabilistic SA, the administration of apremilast before biologicals was dominant in 100% of the simulations (**Figure 2**).

Table 2. One-Way Deterministic Sensitivity Analysis Results

Parameter	Base Case Parameters	Sensitivity Analysis Parameters	Incremental Total Cost (€)	Incremental QALY	ICER (€/QALY)
Base case ICER			-6,545	0.12	Dominant
Time horizon	20 years	10 years	-4,326	0.03	Dominant
		Lifetime (40 years)	-7,372	0.15	Dominant
Discount rate	3%	0%	-8,189	0.17	Dominant
		5%	-5,743	0.09	Dominant
Drug order in biologicals sequence	A >U >E > I	U >A >E >I	-6,595	0.11	Dominant
		E >U >A >I	-6,539	0.11	Dominant
Mean weight of patients	92.63 kg	75 kg	-5,911	0.11	Dominant
Best supportive care cost	€1,358.91	€716.53	0	0.11	Dominant
		€1,562.75	-8,622	0.11	Dominant
Hospitalization from non-responder patients	10 days/year	5 days	-7,336	0.11	Dominant
		15 days	-5,756	0.11	Dominant
Infliximab cost	€406.77	€496.06 (Remicade®)	-7,242	0.11	Dominant

A=adalimumab; E=etanercept; ICER=incremental cost-effectiveness ratio; U=ustekinumab.

Figure 2. Cost-Effectiveness Plane



LIMITATIONS

- Response rates for each treatment within the model were assessed at different time points, and no studies including all current therapies were performed. The model assumes that efficacy is maintained over a long time horizon.
- Due to the lack of studies, utilities have been considered from studies conducted in countries other than Spain. However, based on the experience and knowledge of the experts consulted, this information could also be representative of the Spanish population.
- The present model was developed from a third-party payer perspective; thus it did not include indirect costs that could be useful for a societal analysis.

CONCLUSION

- The administration of apremilast before biologicals resulted in a dominant strategy for the Spanish NHS in the treatment of patients with moderate to severe plaque psoriasis.

REFERENCES

1. Girolomoni G, Griffiths CE, Krueger J, et al. Early intervention in psoriasis and immune-mediated inflammatory diseases: a hypothesis paper. *J Dermatolog Treat.* 2015;26:103-q12.
2. Mayo Foundation for Medical Education and Research. Psoriasis. Available at: http://www.mayoclinic.com/health/psoriasis/DS00193. Accessed October 2015.
3. Maza A, Richard MA, Aubin F, et al. Significant delay in the introduction of systemic treatment of moderate to severe psoriasis: a prospective multicentre observational study in outpatients from hospital dermatology departments in France. *Br J Dermatol.* 2012;167:643–648.
4. European Medicines Agency. EPAR summary for the public. Otezla (apremilast). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/003746/WC500182630.pdf. Accessed September 2015.
5. BOT Plus Web site. Available at: http://www.portalfarma.com. Accessed September 2015.
6. Royal Decree-Law 8/2010. Available at: http://www.boe.es/boe/dias/2010/05/24/pdfs/BOE-A-2010-8228.pdf. Accessed September 2015.
7. eSalud - Información económica del sector sanitario. Available at: http://www.oblikue.com/bddcostes. Accessed September 2015.
8. Lopez-Bastida J, Oliva J, Antonanzas F, et al. Spanish recommendations on economic evaluation of health technologies. *Eur J Health Econ.* 2010;11:513-520.
9. Woolacott N, Hawkins N, Mason A, et al. Etanercept and efalizumab for the treatment of psoriasis: a systematic review. *Health Technol Assess.* 2006;10:1-233; i-iv.

This study was sponsored by Celgene Corporation.

Presented at: the ISPOR 18th Annual European Congress; 7–11 November 2015; Milan, Italy.