



# IL12p40 Antibody Generation, Development and Clinical Data

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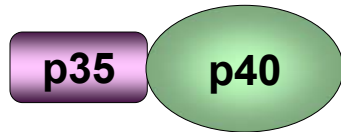
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Director, Biologics Generation  
Abbott

Therapeutic Antibodies and Beyond  
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# Biology of Interleukin-12

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- **First identified hetero-dimeric cytokine**



- **IL-12p70 is produced by monocytes, macrophages, DC and neutrophils**
- **Regulates innate resistance and adaptive immunity**
  - Stimulates NK cells, T cells, DC and macrophages to produce IFN- $\gamma$
  - Promotes the differentiation of naïve CD4<sup>+</sup> T cells into Th1 cells
- **IL-12 may play an important role in autoimmune diseases**
- **Anti-IL-12 antibodies reduce disease severity**
  - EAE (MS model)
  - Colitis (Crohn's disease model)

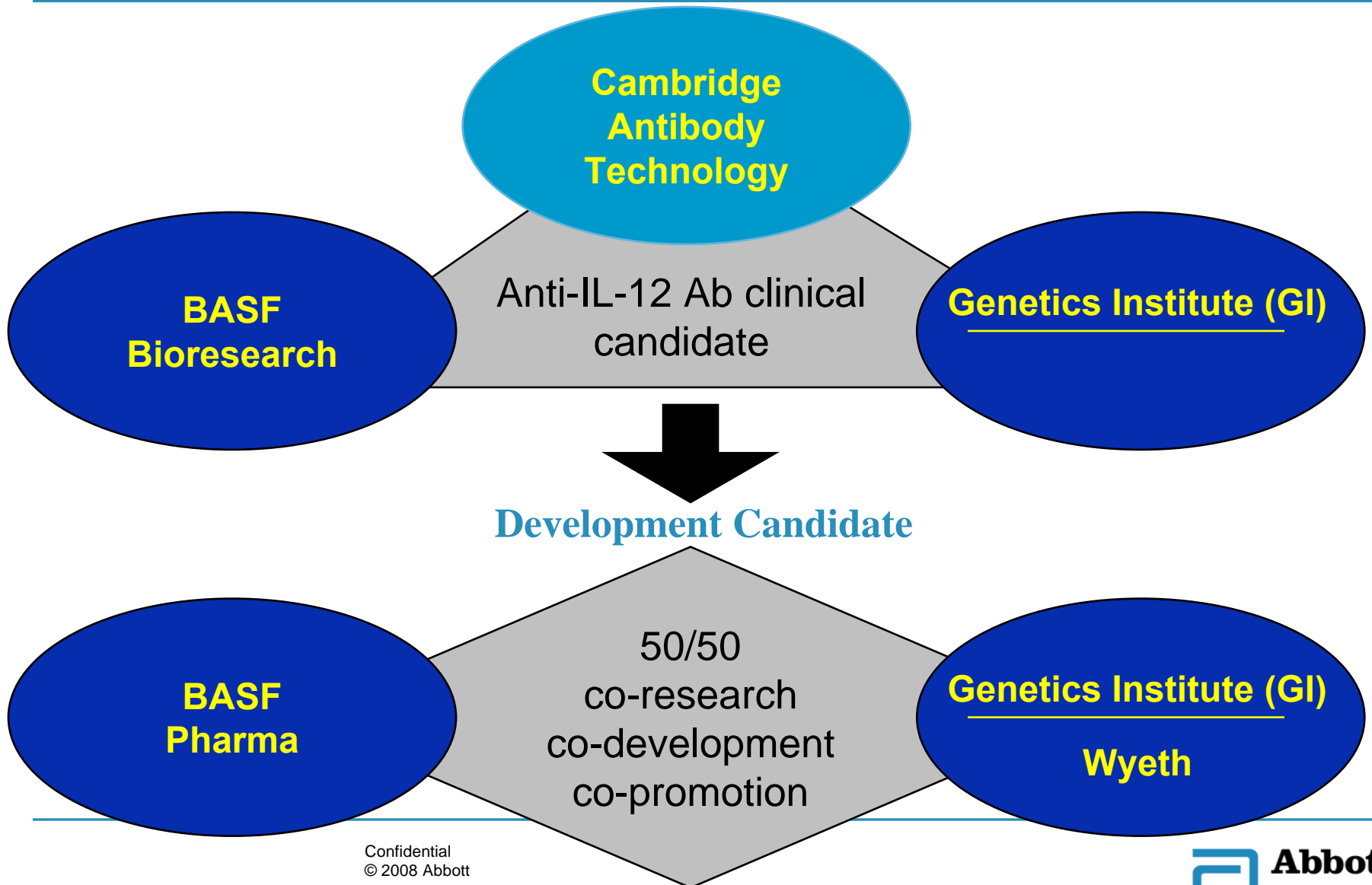
# Around the kitchen table

## at the Kamen/Veldman residence

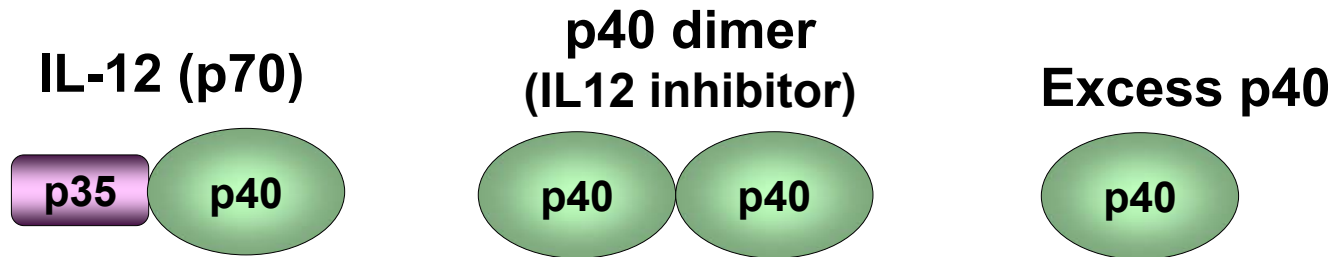
- **Genetics Institute**
  - Is developing the cytokine IL-12 for cancer indications
  - Is interested in an inhibitor to IL-12 for MS
  - Considers starting a small molecule project to block IL-12
- **BASF**
  - Is collaborating with CAT to generate an anti-TNF antibody
  - Has selected IL-12 as a possible next target to work on with CAT
  - Has no reagents or rights to IL-12 or IL-12 antibodies
- **Why don't we do this together?**



# Anti-IL-12 Collaboration Strategy



# Target Product Profile for anti-IL12 mAb



- Antibodies specific for either p40 or p35
  - p35 specific antibody preferred
- Fully human antibody sequence
- Affinity and potency in relevant assays  $10^{-10}$  M
- Lack of reactivity with other cytokines, proteins or tissues
- Binding to cyno orthologue (to enable tox/PK)
- Target and disease validation data in relevant models

# IL-12 Project Milestones CAT/GI/BASF

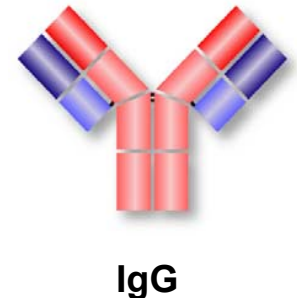
- Milestone 1
  - 4 lineages of scFv that specifically bind IL-12
- Milestone 2
  - 2 lineages of scFv that inhibit IL-12 bioactivity by 10%
  - One specific for p35, the other one specific for p40



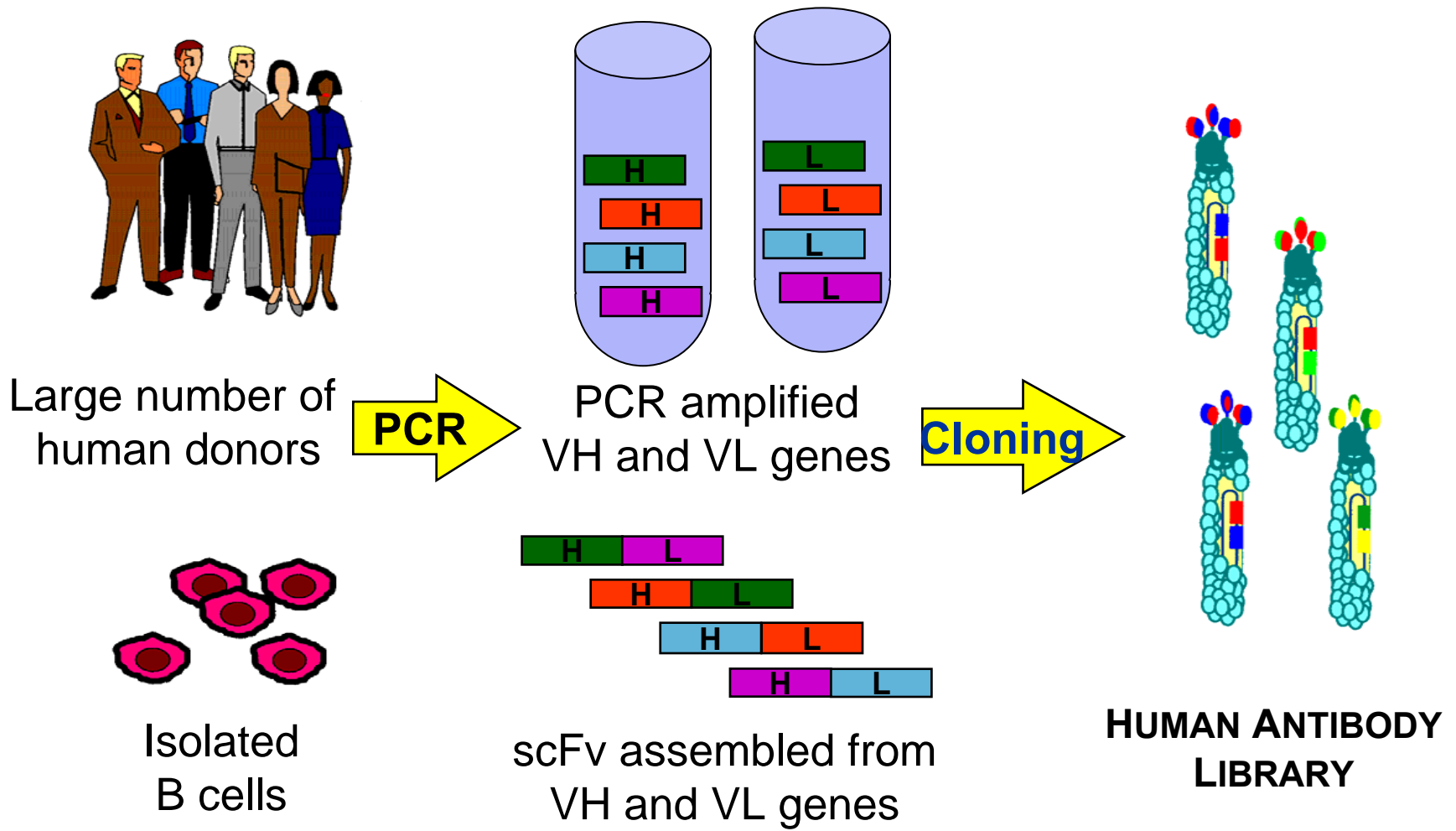
p35

p40

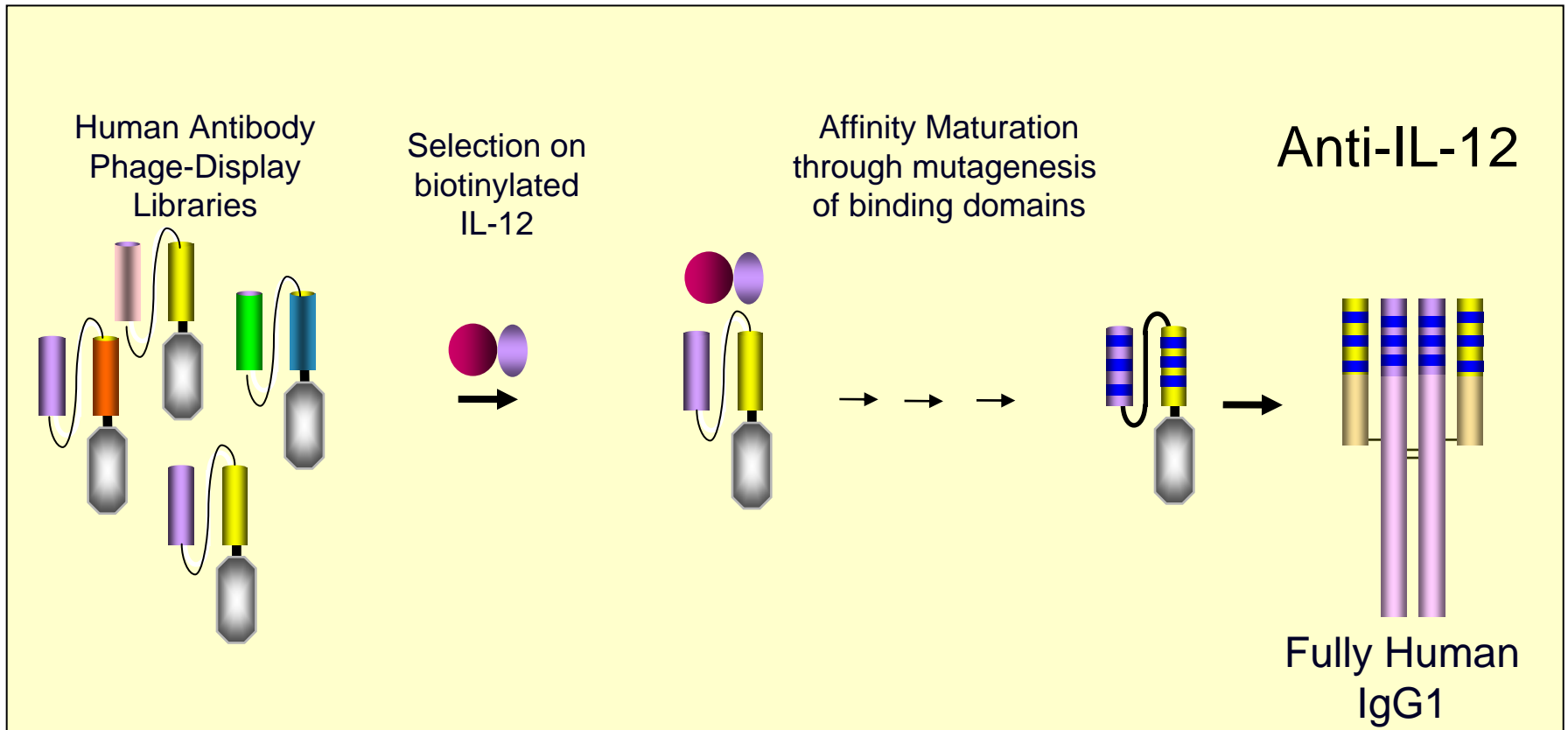
- Milestone 3a
  - full length IgG
  - specific for p35
  - IC50 < 10 nM
- Milestone 4a
  - specific for **p35**
  - IC50 < **100 pM**
- Milestone 3b
  - full length IgG
  - specific for p40
  - IC50 < 10 nM
- Milestone 4b
  - specific for **p40**
  - IC50 < **100 pM**



# Cambridge Antibody Technology: Phage Display of Human Antibody Libraries



# Generation of Anti-IL-12 Antibody Selection and Affinity Maturation



# Affinity Maturation

- CDR Spiking - VH and VL
- Combination of best heavy chain and light chain clones
- Randomization of VH and VL CDR3

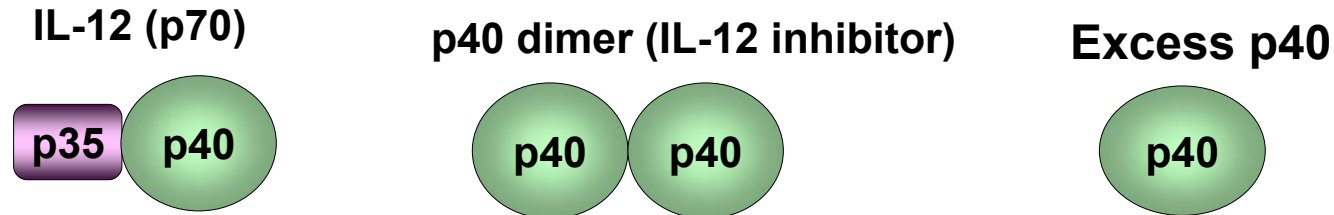
Clone	H3	L3	PHA assay IC50	k off
Joe-9	CTT SGSYDY	QSYDSSLRGSRV	1.00 E-06	1.0 E-1
70-1	CTT HGSHDN	QSYDSSLRGSRV	2.00 E-07	1.3 E-2
103-14	CKT HGSHDN	QSYERGFTGSMV	1.20 E-09	6.7 E-4

- Attempts to isolate p40 clones  $< 1$  nM by phage display fail due to stickiness of high affinity clones
  - Screening of 1000+ scFv clones by Biacore for improved off-rate identified Y61 (200 pM)
- p35 specific lineage not successful

# Should We Focus on Anti-p35 or Anti-p40?

IL-12p70 is biologically active, p40 dimer is inhibitory

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- Anti-mouse p40 antibodies are efficacious in EAE and TNBS colitis
- Will an anti-p35 antibody be more potent than anti-p40 in vivo?
- Compare anti-mouse p40 and anti-mouse p35 antibodies in vivo
  - DTH response
  - Colitis model in mice

# Better Efficacy with Potent anti-p40 Antibody

Antibody	Epitope	Bioassay IC50 pM	<i>In vivo</i> efficacy DTH/colitis
C17.15	Mouse p40	20	good/good
C18.2	Mouse p35	300	none/poor
Y61	Human p40	150-200	

- Anti-p40 antibody is most efficacious
- Use C17.15 as gold standard for anti-human p40 antibody
- Project goal change:
  - Stop work on p35 lineage
  - Collaborate with CAT to improve Y61 to 20 pM

# Improving Y61

## Affinity Maturation by Targeting CDR “Hot-Spots”

Phage display not an option - use targeted mutagenesis instead

- CDR positions that are frequently antigen contact sites

MacCallum et al., J. Mol. Biol., 1996

- Natural high-frequency somatic mutation sites

Tomlinson et al., J. Mol. Biol., 1996

- Each ‘hot-spot’ position mutated to all 20 amino acids

– Individual clones tested: BIAcore & bioassays

	CDR H1										CDR H2										CDR H3													
Kabat Number	27	28	29	30	31	32	33	34	35		50	51	52	52A	53	54	55	56	57	58	59	60	61	62	63	64	65		95	96	97	98	101	102
Y61 VH	F	I	F	S	S	Y	G	M	H		F	I	R	Y	D	G	S	N	K	Y	Y	A	D	S	V	K	G		H	G	S	H	D	N

	CDR L1										CDR L2						CDR L3																	
Kabat number	24	25	26	27	27A	27B	28	29	30	31	32	33	34		50	51	52	53	54	55	56		89	90	91	92	93	94	95	95A	95B	95C	96	97
Y61 VL	S	G	G	R	S	N	I	G	S	N	T	V	K		G	N	D	Q	R	P	S		Q	S	Y	D	R	G	F	H	P	A	L	L



# J695

## Summary of *In Vitro* Characterization

Antibody	Affinity BIAcore			Potency IC50 (pM)	
	On Rate ( $M^{-1} s^{-1}$ )	Off Rate ( $s^{-1}$ )	Kd (pM)	Receptor Binding	PHA blast proliferation
C17.15	$3.8 \times 10^5$	$1.8 \times 10^{-4}$	480	150	14
<b>J695</b>	<b><math>3.8 \times 10^5</math></b>	<b><math>3.7 \times 10^{-5}</math></b>	<b>97</b>	<b>11</b>	<b>5.8</b>

BASF/Genetics Institute Jointly Approve J695 as  
Development Candidate

# Anti-p40 versus Anti-p35

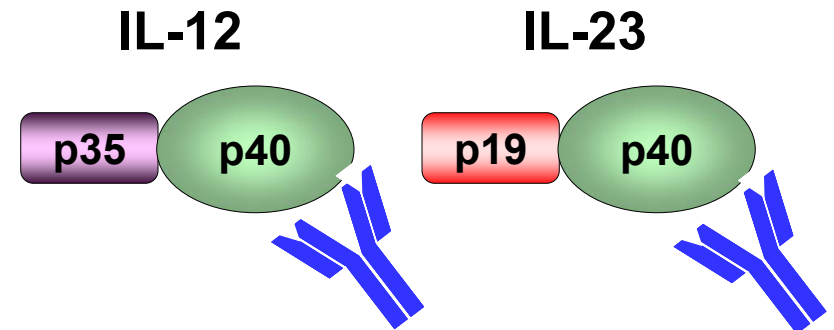
Now we understand why anti-p40 is more efficacious!

- November 2000 DNAX describes IL-23

**Novel p19 Protein Engages IL-12p40 to Form a Cytokine, IL-23, with Biological Activities Similar as Well as Distinct from IL-12**

- 2003 Nature paper - Cua et al.

**Interleukin-23 rather than interleukin-12 is the critical cytokine for autoimmune inflammation of the brain**



**J695 Binds/Neutralizes IL-12 and IL-23**

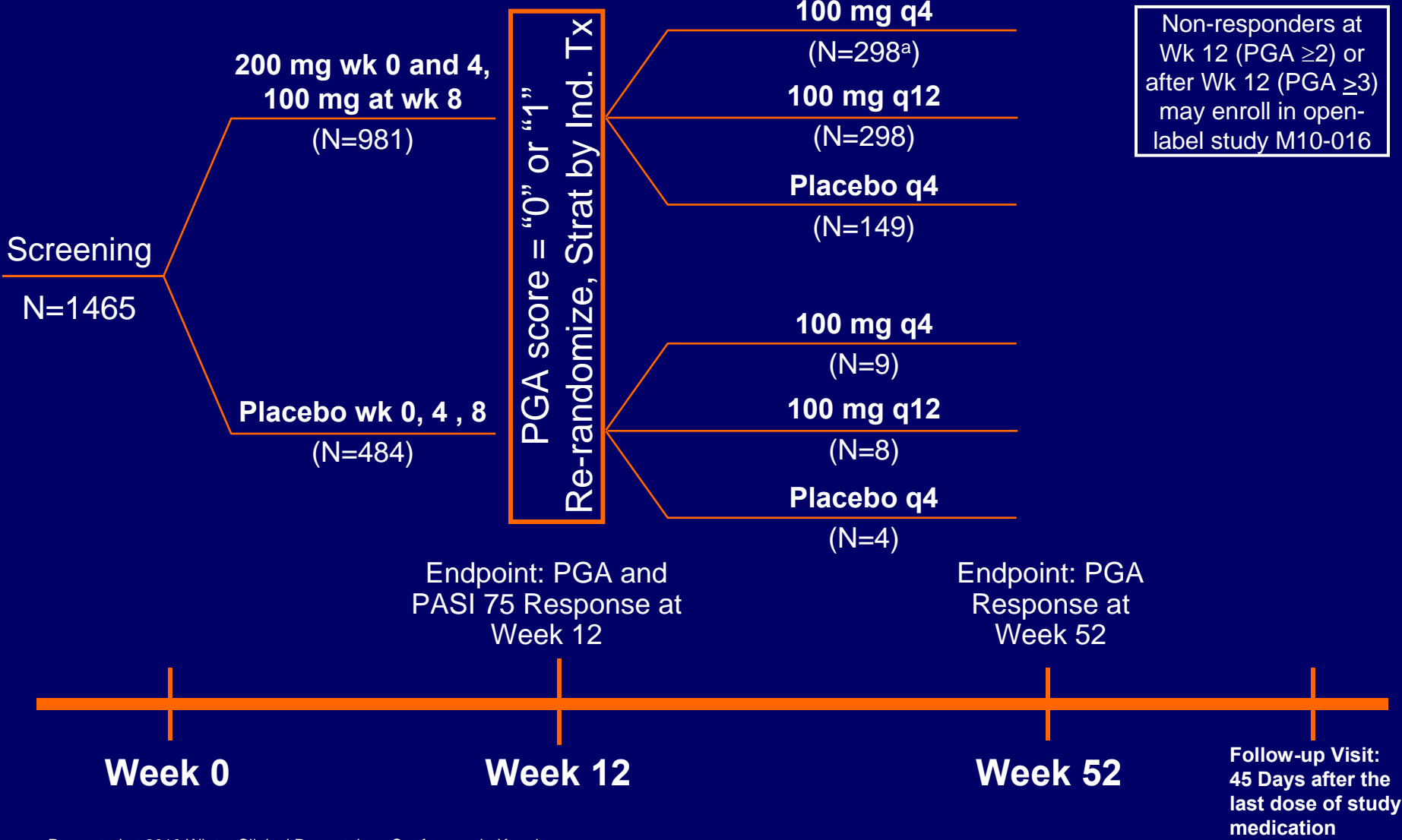
# Clinical Studies with ABT-874 (J695)

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- Phase I in healthy volunteers
  - Terminal phase half-life about 9 days
- Phase II studies in RA, Crohn's disease and MS did not meet clinical endpoints
- Phase II and III studies in Psoriasis
  - All clinical endpoints met
  - Data of pivotal phase III study summarized

**M06-890: Efficacy and Safety Results from  
the Phase III, Randomized Controlled  
Trial Comparing Two Dosing Regimens  
of ABT-874 to Placebo in Patients with  
Moderate to Severe Psoriasis**

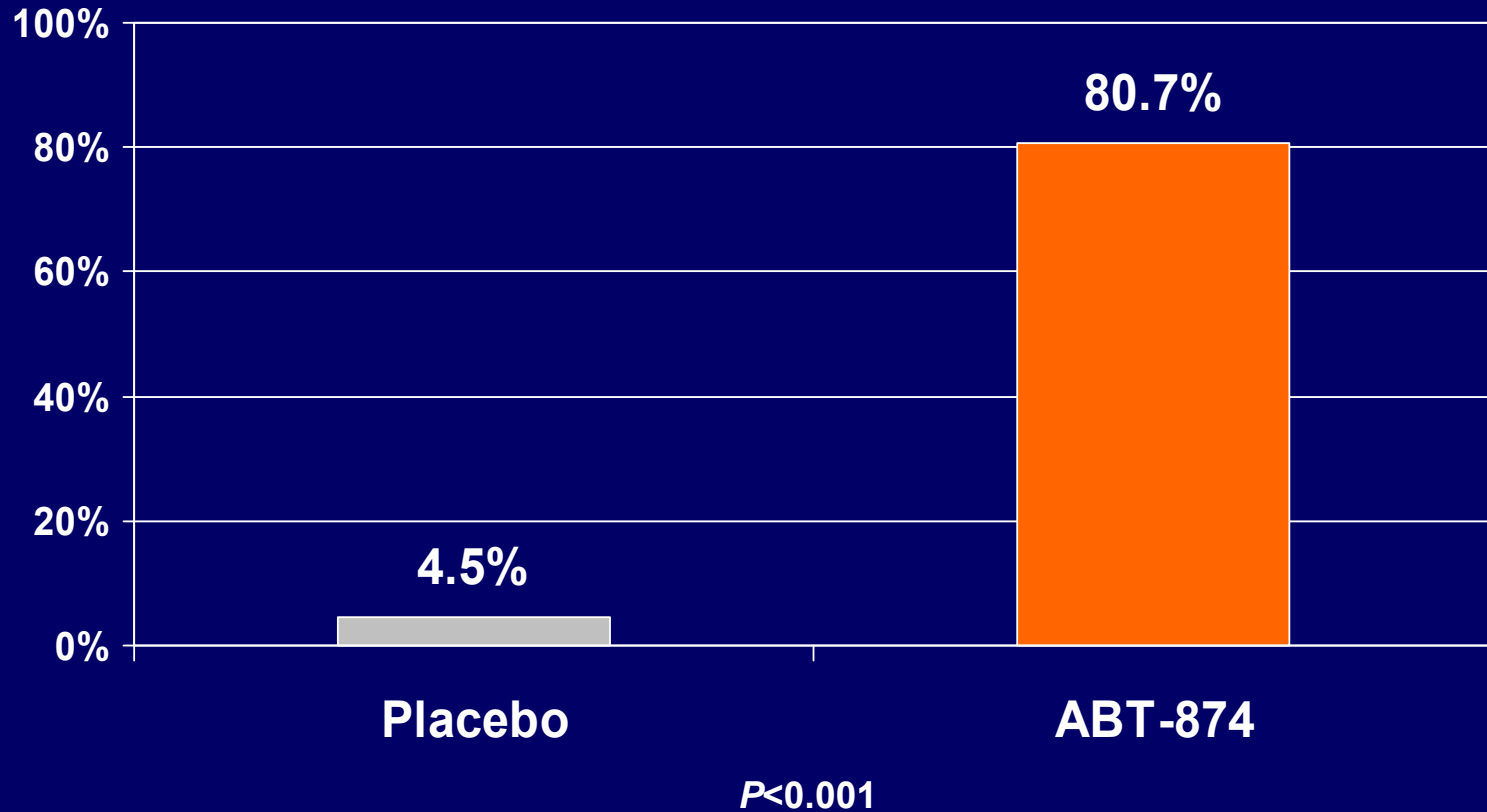
# Study Design



Non-responders at Wk 12 (PGA  $\geq 2$ ) or after Wk 12 (PGA  $\geq 3$ ) may enroll in open-label study M10-016

<sup>a</sup> One subject in Q4 group was re-randomized but did not receive any study drug in Maintenance Phase.

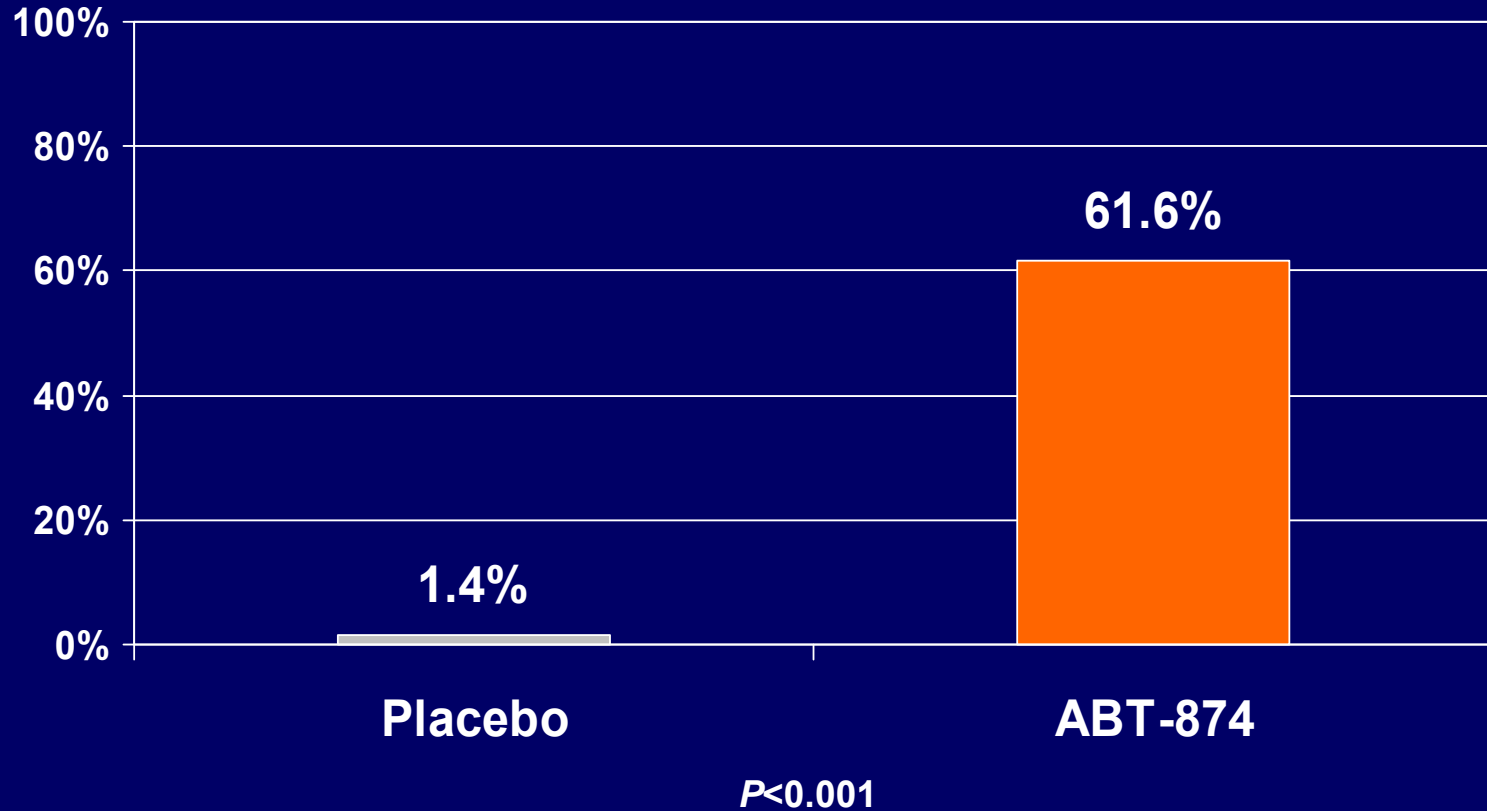
# PASI 75 Response at Week 12



**PASI – Psoriasis Area and Severity Index**

**Non-responder imputation analysis: Patients with missing PASI scores were considered non-responders**

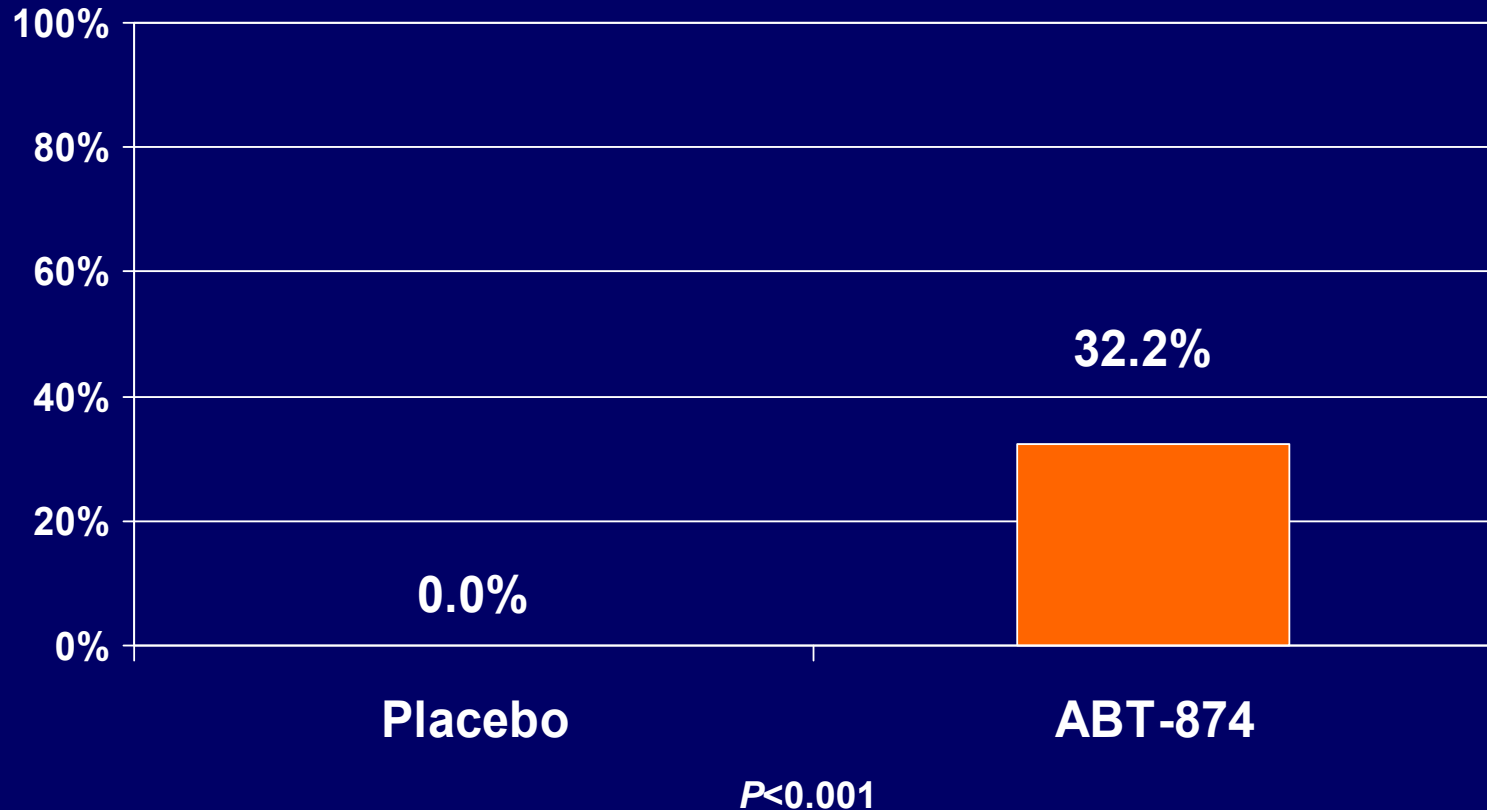
# PASI 90 Response at Week 12



**PASI – Psoriasis Area and Severity Index**

**Non-responder imputation analysis: Patients with missing PASI scores were considered non-responders**

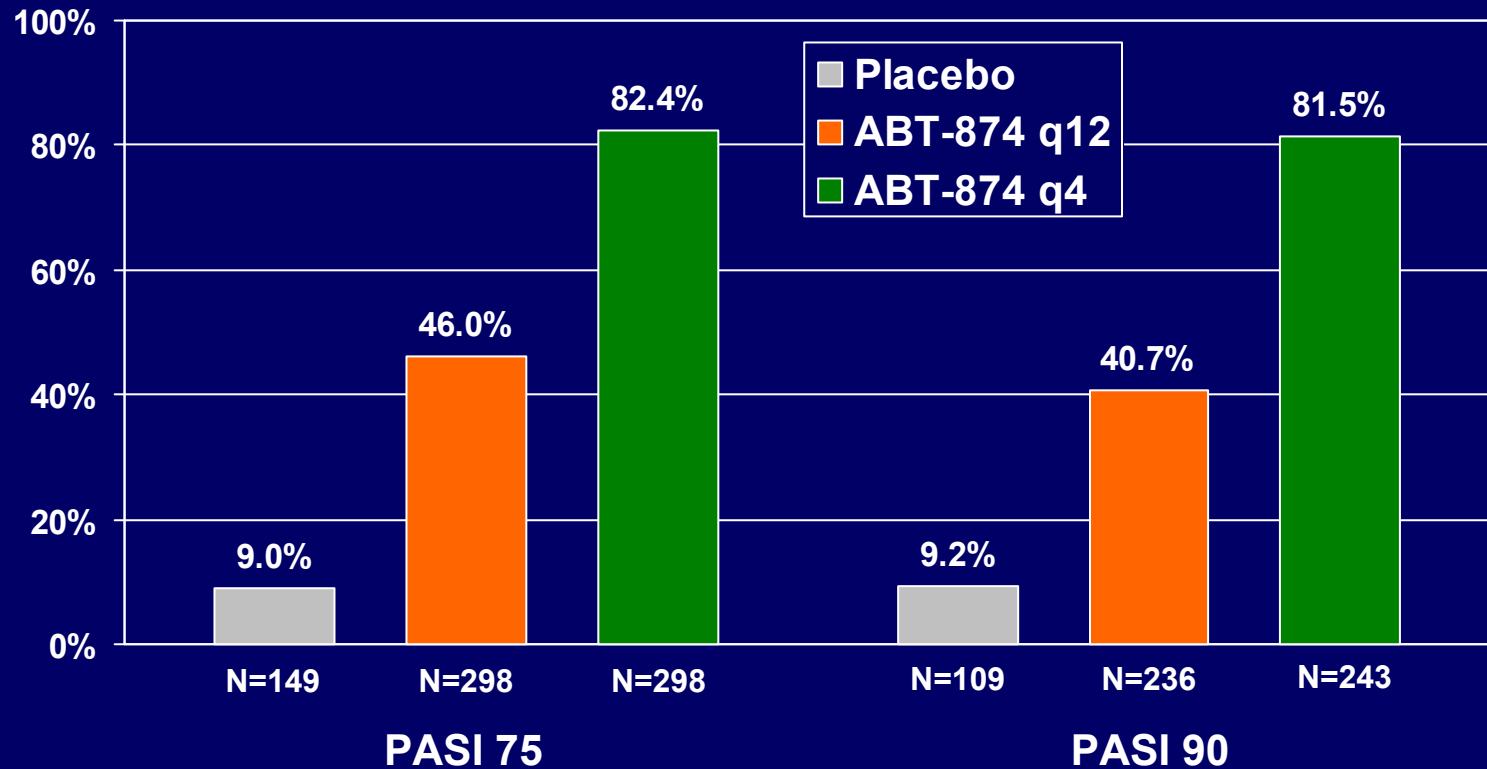
# PASI 100 Response at Week 12



**PASI – Psoriasis Area and Severity Index**

**Non-responder imputation analysis: Patients with missing PASI scores were considered non-responders**

# PASI 75 and PASI 90 Response at Week 52 in Week 12 PGA 0/1 Responders



\* Percentages of patients in each treatment group who achieved PASI 75 and PGA 0/1 at Week 12 and maintained PASI 75 at Week 52.  
 # Percentages of patients in each treatment group who achieved PASI 90 and PGA 0/1 at Week 12 and maintained PASI 90 at Week 52.  
 Intent-to-treat analysis: Patients with missing PASI scores were considered non-responders.  
 P<0.001 for all time points (between each ABT-874 dosing group and placebo, and between ABT-874 dosing groups).

# Most Common Adverse Events That Were Reported at $\geq 5\%$

	Induction Phase		Maintenance Phase			All ABT-874 (N=998) <sup>a</sup>
	ABT-874 (N=981)	Placebo (N=484)	ABT-874 q4 (N=297)	ABT-874 q12 (N=298)	Placebo (N=149)	
	n (%)					
Nasopharyngitis	63 (6.4)	20 (4.1)	39 (13.1)	35 (11.7)	9 (6.0)	106 (10.6)
Headache	53 (5.4)	9 (1.9)	0	0	0	66 (6.6)
Upper respiratory tract infection	49 (5.0)	20 (5.0)	48 (16.2)	24 (8.1)	8 (5.4)	104 (10.4)
Back pain	0	0	16 (5.4)	6 (2.0)	3 (2.0)	<5%

<sup>a</sup>All patients randomized to ABT-874 in the Induction Phase and re-randomized to ABT-874 in the Maintenance Phase.

# Adverse Events of Interest

	Induction Phase		Maintenance Phase		
	ABT-874 (N=981)	Placebo (N=484)	ABT-874 q4 (N=297)	ABT-874 q12 (N=298)	Placebo (N=149)
	n (%)				
<b>Any AE</b>	<b>517 (52.7)</b>	<b>229 (47.3)</b>	<b>215 (72.4)</b>	<b>183 (61.4)</b>	<b>86 (57.7)</b>
<b>Any AE leading to discontinuation of study drug</b>	<b>17 (1.7)</b>	<b>4 (0.8)</b>	<b>3 (1.0)</b>	<b>6 (2.0)</b>	<b>1 (0.7)</b>
<b>Any serious AE</b>	<b>20 (2.0)</b>	<b>6 (1.2)</b>	<b>4 (1.3)</b>	<b>9 ( 3.0)</b>	<b>2 (1.3)</b>
<b>Deaths</b>	<b>1<sup>a</sup></b>	<b>0</b>	<b>0</b>	<b>0<sup>b</sup></b>	<b>0</b>
<b>AEs of special interest:</b>					
<b>Any infection</b>	<b>219 (22.3)</b>	<b>96 (19.8)</b>	<b>132 (44.4)</b>	<b>107 ( 35.9)</b>	<b>41 ( 27.5)</b>
<b>Serious infections</b>	<b>5 (0.5)</b>	<b>1 (0.2)</b>	<b>0</b>	<b>2 (0.7)</b>	<b>1 (0.7)</b>
<b>Malignancies</b>	<b>6 (0.6)</b>	<b>0</b>	<b>3 (1.0)</b>	<b>5 (1.7)</b>	<b>0</b>
<b>SCC</b>	<b>4 (0.4)</b>	<b>na</b>	<b>0</b>	<b>2 (0.7)</b>	<b>na</b>
<b>BCC</b>	<b>0</b>	<b>na</b>	<b>2 (0.7)</b>	<b>2 (0.7)</b>	<b>na</b>
<b>Other</b>	<b>2 (0.2)<sup>c</sup></b>	<b>na</b>	<b>1 (0.3)<sup>d</sup></b>	<b>1 (0.3)<sup>e</sup></b>	<b>na</b>
<b>Cardiovascular</b>	<b>5 (0.5)<sup>f</sup></b>	<b>0</b>	<b>1 (0.3)<sup>g</sup></b>	<b>1 (0.3)<sup>h</sup></b>	<b>0</b>
AE = adverse event; SCC = squamous cell carcinoma; BCC = basal cell carcinoma; na = not applicable.					



# Conclusions

- ABT-874 induced rapid and significantly higher efficacy responses in patients with moderate to severe psoriasis compared to placebo
- Dosing ABT-874 every 4 weeks resulted in better maintenance of response than every 12 weeks
- A higher incidence of infection and skin malignancy adverse events were observed in ABT-874 vs. placebo treated patients. Considering the immunomodulating mechanism of ABT-874, these findings are not unexpected and support the need for close monitoring and surveillance for these events
- A numerical imbalance was observed for MACE events, with 7 cases reported in the ABT-874 group compared with no events in the placebo group. While cardiovascular events are not unexpected in a psoriasis patient population with underlying CV risk factors, and all 7 patients had CV risk factors, further evaluation and research is essential to determine if this increase in the number of MACE events is a reproducible phenomenon in patients treated with ABT-874

# Acknowledgement

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- Cambridge Antibody Technology
  - Alex Duncan and phage display team
- Genetics Institute/Wyeth
  - Veldman lab
- BASF Bioresearch Center/Abbott
  - Jochen Salfeld lab
  - Martin Kaul and Global Project Team