Pipeline: Respiratory, Inflammation & Autoimmunity (RIA)

Inhaled therapeutic leadership; spearheading immunology biologics

Bing Yao, Head of MedImmune Respiratory, Inflammation & Autoimmunity iMED

Respiratory: Transform patient outcomes in asthma, COPD & IPF

Respiratory:
Industry-leading portfolio

Phase I

Small molecule

- **AZD1419** TLR9 *asthma*
- **AZD7624** ip38 *COPD*
- **AZD7594** iSGRM *asthma*
- **AZD7594** iSGRM *COPD*
- **PT010** LAMA/LABA/ICS *asthma*
- **AZD8999** MABA *asthma*
- **AZD8999** MABA *COPD*

Phase II

Large molecule

- **brodalumab*** IL17R *asthma*
- **AZD9412** Inhaled IFNβ *COPD*
- **tralokinumab** IL13 *IPF*
- **MEDI9929*** TSLP *asthma*
- **AZD9412** Inhaled IFNβ *asthma*

Small molecule

- **AZD2115** MABA *COPD*
- **PT008** ICS *asthma*
- **AZD0548** (abediterol) LABA *asthma*
- **AZD0548** (abediterol) LABA *COPD*
- **PT010** LAMA/LABA/ICS *COPD*
- **PT009** ICS/LABA *COPD*

Phase III / Registration

Large molecule

- **benralizumab** IL5R *severe asthma*
- **tralokinumab** IL13 *severe asthma*
- **benralizumab** IL5R *COPD*

Small molecule

- **PT003** LAMA/LABA *COPD*
- **PT001** LAMA *COPD*
- ***Duaklir*** LAMA/LABA *COPD*

Marketed

Symbicort® Pulmicort® Eklira® Genuair® aclidinium bromid

Disease area

- Asthma
- COPD
- IPF

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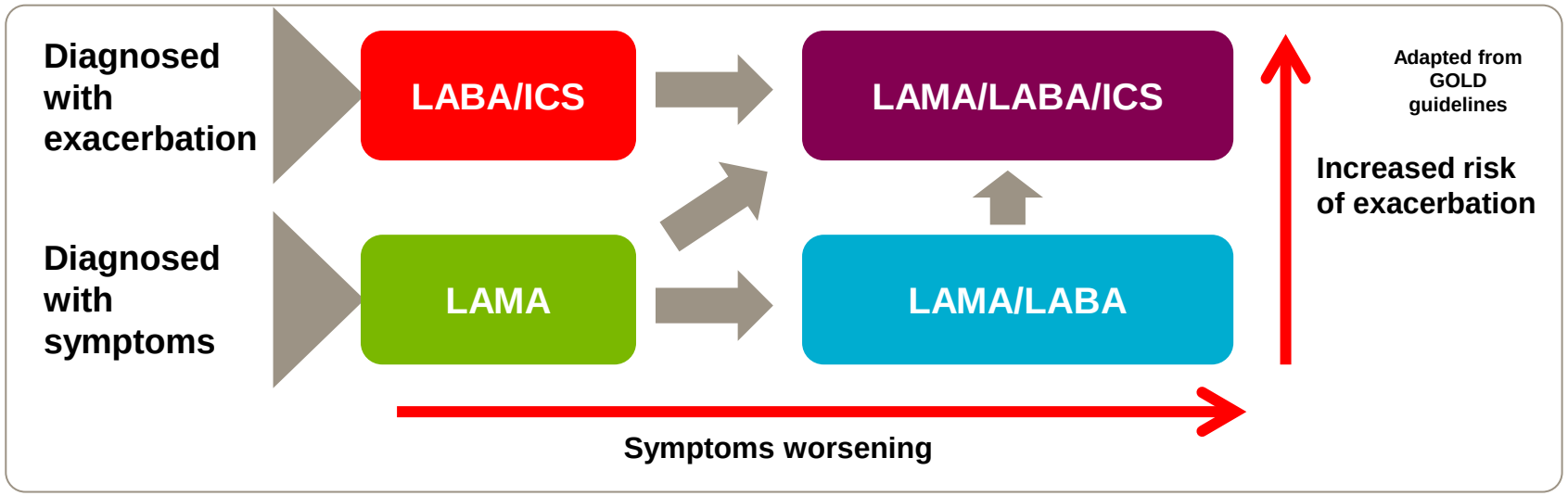
COPD: Inhaled portfolio addresses all disease severities and provides device choice



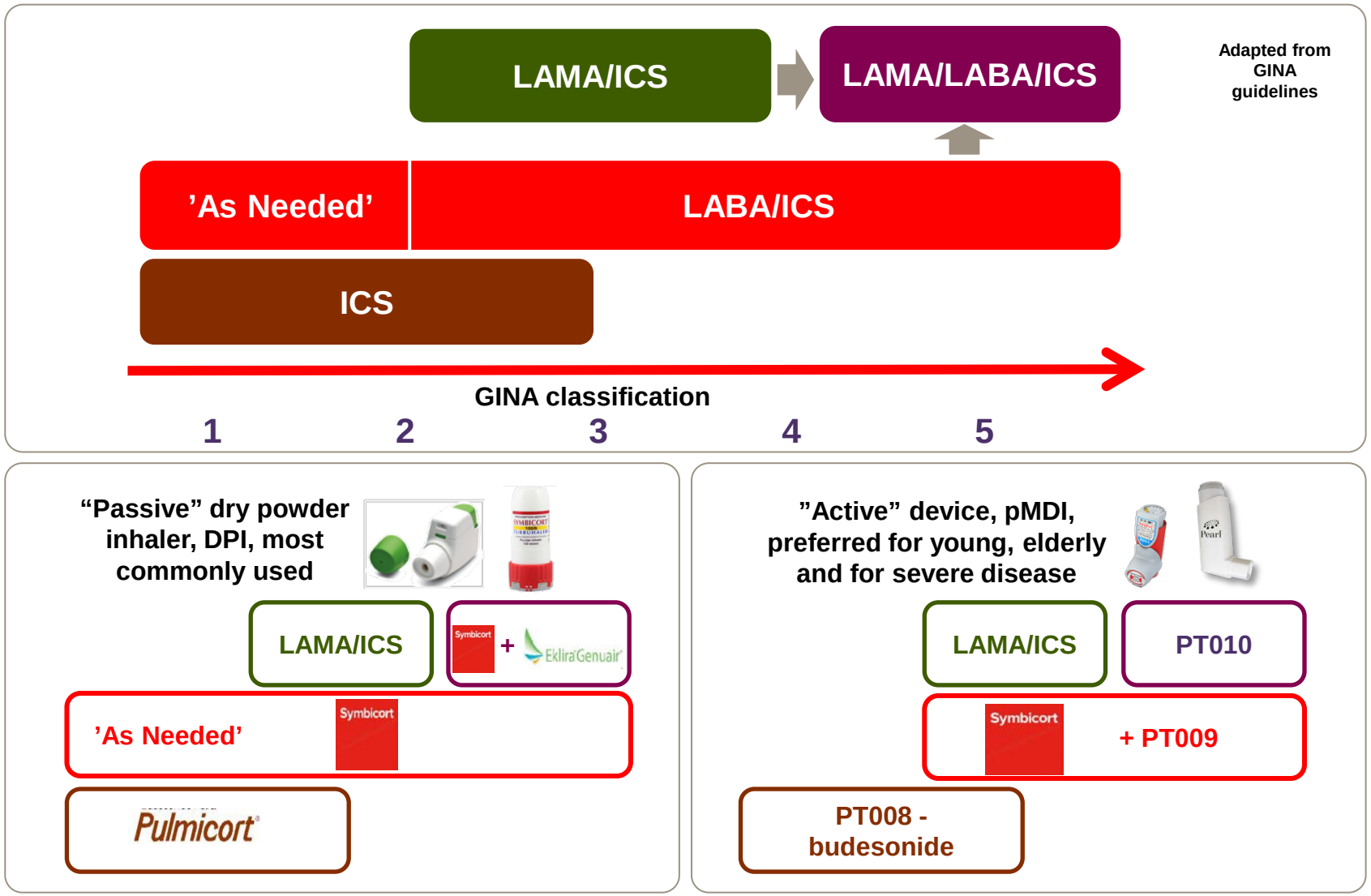
"Passive" dry powder inhaler, DPI, most commonly used

- Symbicort
- Symbicort + Eklira Genuair
- Eklira Genuair
- Duaklir Genuair

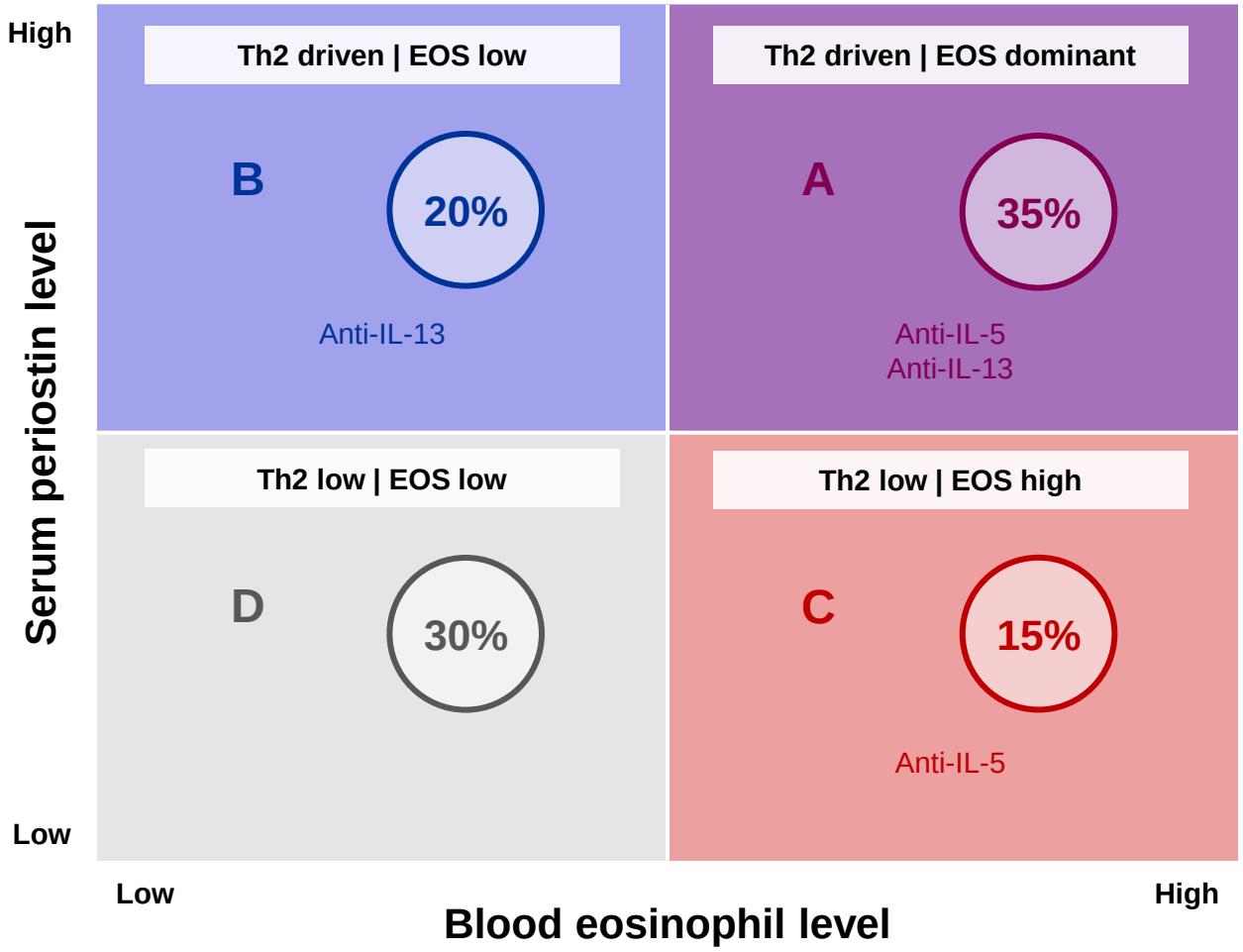
"Active" device, pMDI, preferred for elderly and for severe disease

- Symbicort + PT009
- PT010
- PT001
- PT003

Asthma: Inhaled portfolio addresses all GINA steps and provides device choice



Severe asthma:
Targeting distinct patient subsets

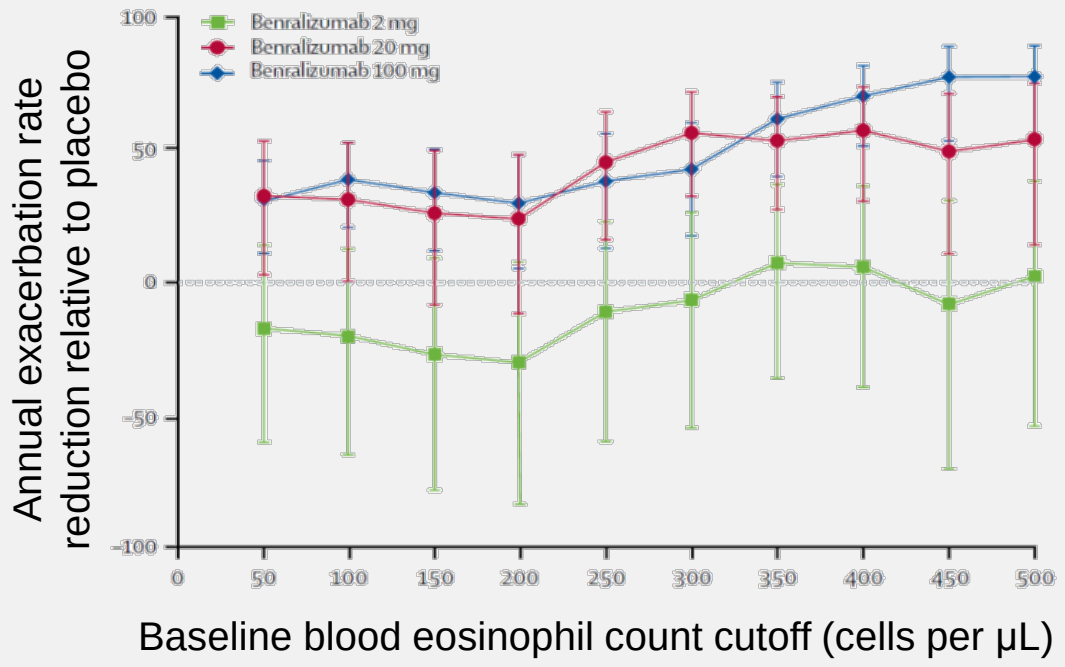


Benralizumab (severe asthma): Only IL5 receptor mAb in Phase III

Phase IIb data

- Potent reduction in eosinophils
- Reduction in asthma exacerbation
- Improvement in lung function

Exacerbation rate reduction



Regulatory submission expected 2016

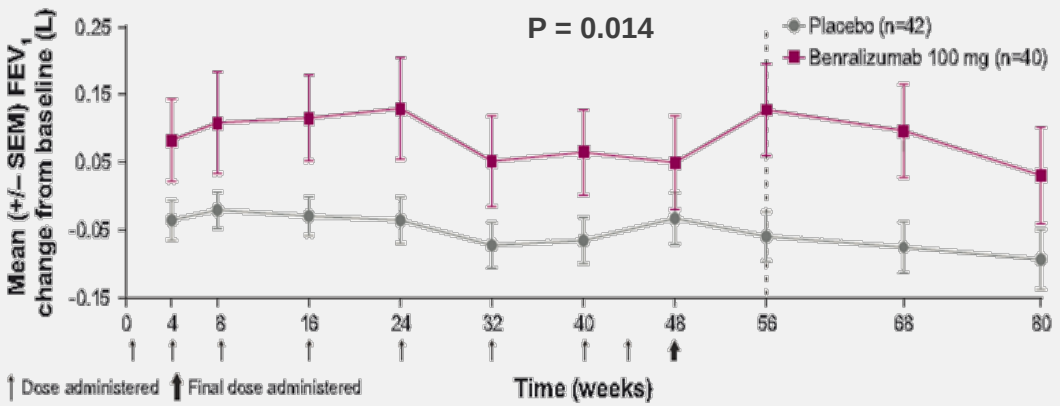
Source: M. Castro et al., Lancet Resp Med, 2014

Benralizumab (COPD): First mAb to show eosinophilic inflammation reduction

Phase IIa data

- First anti-IL5 / IL5R to demonstrate lung function improvement
- Primary endpoint not achieved, but trend toward reduction of exacerbations with elevated eosinophils
- Improvement in symptom scores

Mean change from baseline in FEV1 over time (PP population)



Phase III on track for completion 2018

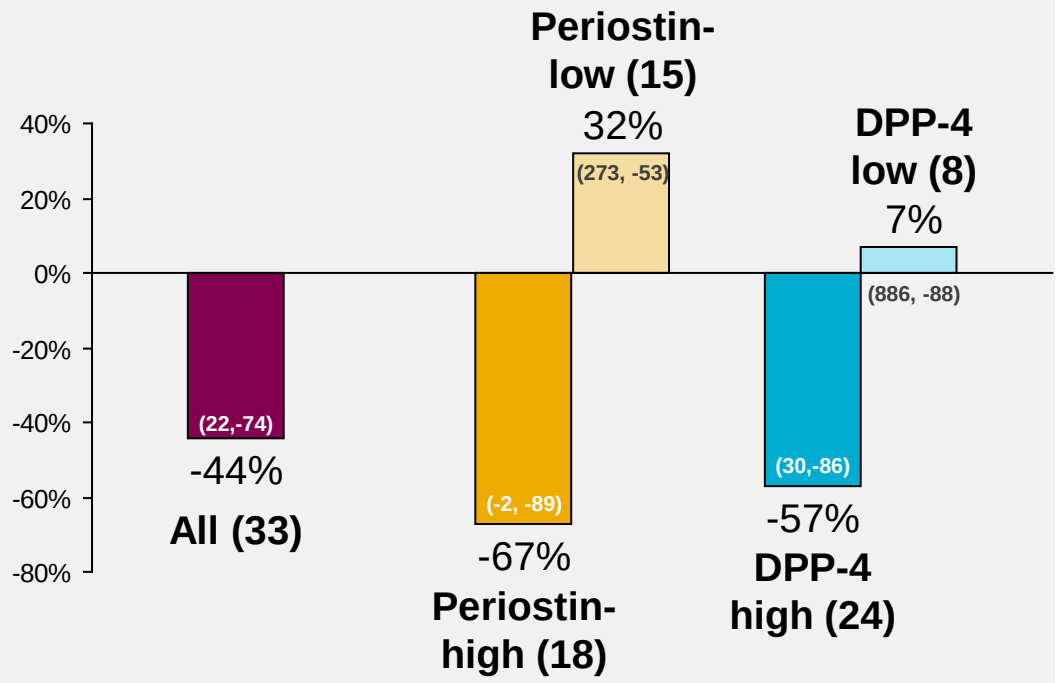
Source: Brightling et al., Lancet Resp Med, 2014

Tralokinumab (severe asthma): Targeting IL13, a central TH2 cytokine

Phase IIb data

- Identified potential responder population
- Identified promising biomarkers
- Efficacy across AER, FEV1, ACQ-6 and AQLQ in subgroups

AER for tralokinumab 300 mg Q2W vs placebo over 52 weeks



Phase III on track for completion 2017
Phase II ongoing in IPF

AER – Asthma Exacerbation Rate, FEV1 – Forced Expiratory Volume in 1 second, ACQ-6 – Asthma Control Questionnaire, AQLQ – Asthma Quality of cycle Questionnaire

Inflammation & Autoimmunity: Series of first & best-in-class assets

Phase I	Phase II		Phase III / Registration	
Large molecule	Large molecule	Small molecule	Large molecule	Small molecule
MEDI5872* B7RP1 *SLE*	mavrilimumab GM-CSFR *rheum arthritis*	RDEA3170 SURI *gout*	brodalumab* IL17R *psoriatic arthritis*	lesinurad SURI *gout*
MEDI4920 CD40L *Sjögren's*	sifalimumab IFNa *SLE*		brodalumab* IL17R *psoriasis*	
MEDI-551 CD19 *MS*	anifrolumab IFNaR *SLE*			
	MEDI7183* α4β7 *Crohn's disease*			
	MEDI7183* α4β7 *ulcerative colitis*			
	MEDI2070* IL23 *Crohn's disease*			

Disease area

- Rheumatology
- Dermatology
- Gastroenterology
- Neuroscience

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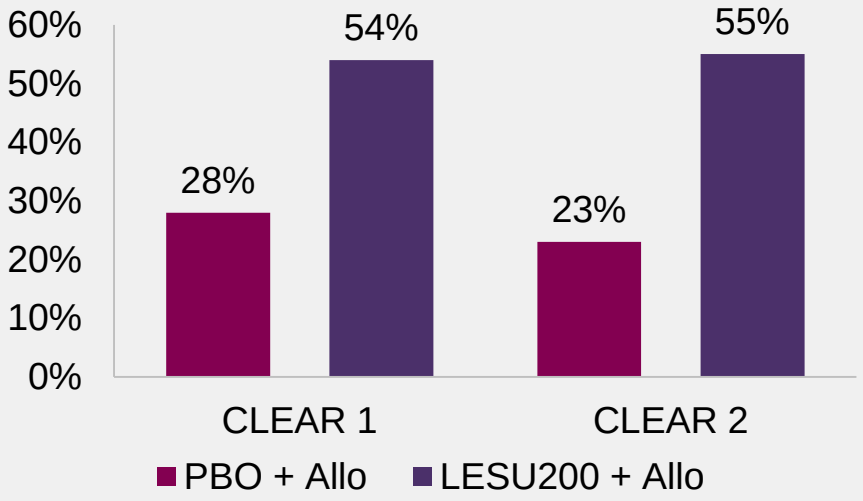
Lesinurad (gout): Progressing to regulatory submission

ACR 2014 late-breaker

Lesinurad in gout

- Gout affects ~15m patients
  - Potential to cause bone, joint, kidney damage and associated with CV disease and its co-morbidities
- Xanthine oxidase (XO) inhibitors act to control production of uric acid
- 40–70% of patients are not at goal on XO inhibitors alone
- Lesinurad and RDEA3170 increase excretion of uric acid
- RDEA3170 Ph II studies progressing with focus in mono and FDC
- **Lesinurad EU / US submission planned Q4 2014 for use w/XO**

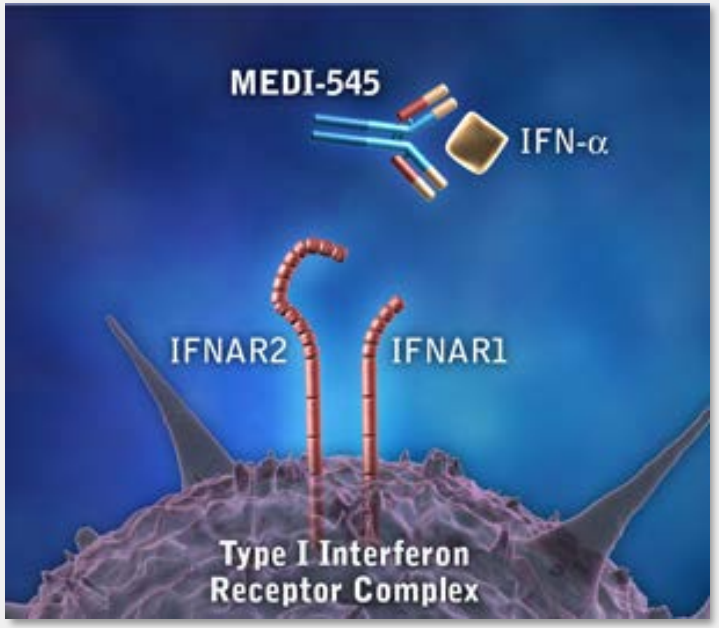
CLEAR 1 and CLEAR 2: Proportion of patients achieving sUA <6 mg/dL at Month 6 – NRI



- AE profile, incl. renal AE of lesinurad 200mg+allopurinol comparable to allopurinol alone
- Increases in serum creatinine observed lesinurad 200mg plus allopurinol vs. allopurinol alone (5.9-6.0% vs. 1.0-3.4%, >1.5x increase vs. baseline)

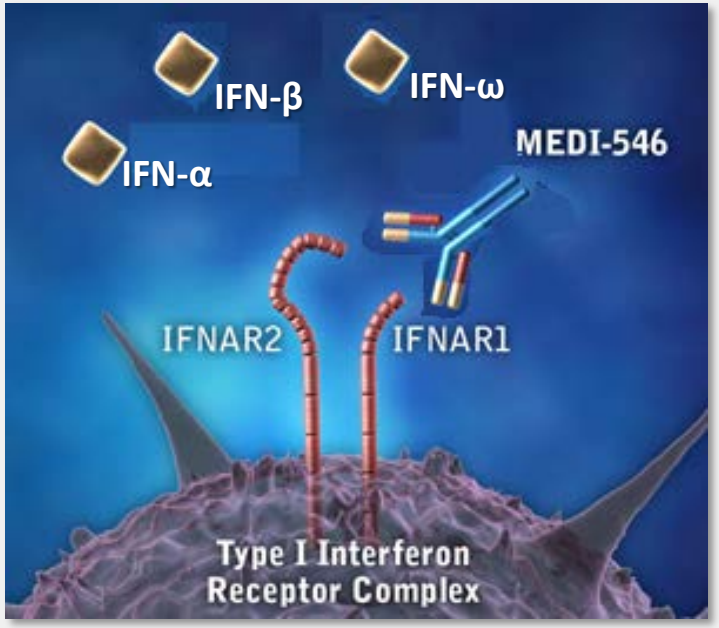
Targeting IFNα / IFNαR in lupus

Sifalimumab binds directly to IFNα neutralising IFNα subtypes



Phase IIb lupus study validates interferon targeting: Primary and secondary endpoints achieved

Anifrolumab targeting broader spectrum of interferons (IFNα, IFNβ, and IFNω)



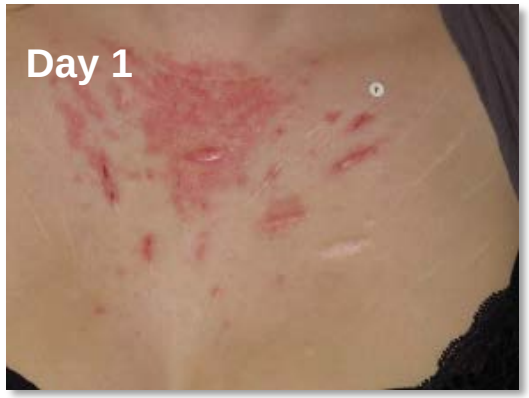
Receptor-targeting potentially better efficacy: Greater PD suppression (70–90% vs. 30–40% for sifalimumab)

Anifrolumab Phase II presentation expected mid-2015
Phase III start expected 2015

Sifalimumab (lupus): Significant improvement in SLE responder index and organ specific measurements

ACR 2014 late-breaker

	Endpoint at day 365		
	SRI (4)	SRI (6)	SRI (8)
All-comers population			
Placebo (%) (N=98 - 108)	45.4	37.4	24.5
1200 mg dose (%), (N=98 - 107)	59.8	53.3	41.8
Effect size (%)	14.4	15.9	17.3
P-value*	0.031	0.016	0.008
Dx+ population			
Placebo (%), (N=79 - 88)	42.0	33.3	20.3
1200 mg dose (%), (N=80 - 87)	57.5	51.7	41.3
Effect size (%)	15.4	18.4	21.0
P-value*	0.038	0.012	0.004



24.5% treatment difference in CLASI-4 response
1200 mg dose vs placebo**

SRI(x) SLE Responder Index(x=reduction in SLEDAI required for response)
*P-value < 0.098 is considered to be statistically significant for the final analysis after adjusting for the interim analysis using O'Brien-Fleming type Lan-DeMets alpha spending function approach to control type I error rate at 0.1 for the primary endpoint
**mITT Population with a CLASI Activity Score ≥10 at Baseline

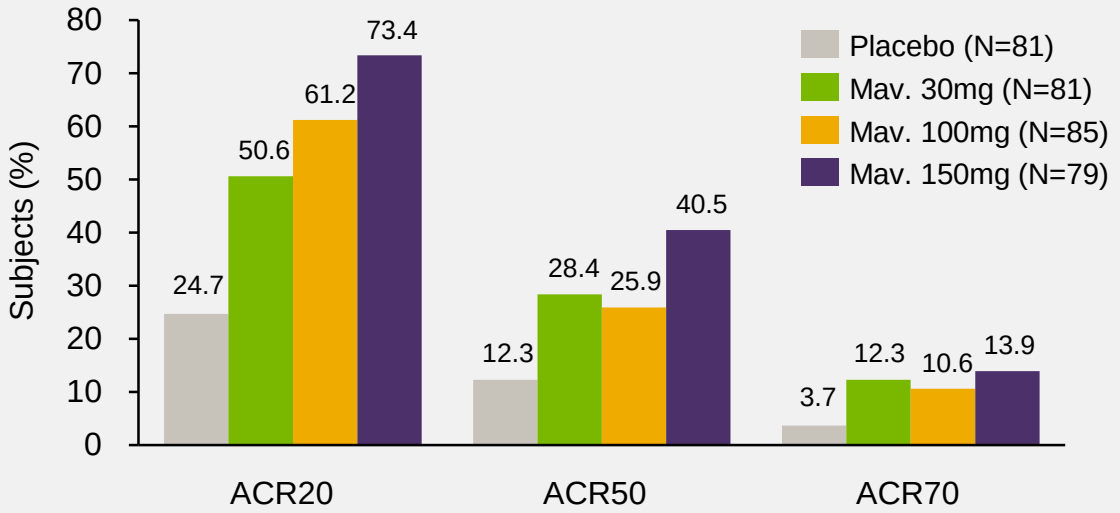
Mavrilimumab (RA): First-in-class anti-GM-CSFRα antibody

ACR 2014 oral presentation

Phase IIb data

- 45–74% of patients on anti-TNF fail to achieve an ACR50
- Mavrilimumab inhibits macrophage activation, differentiation and survival

ACR efficacy responses at day 169

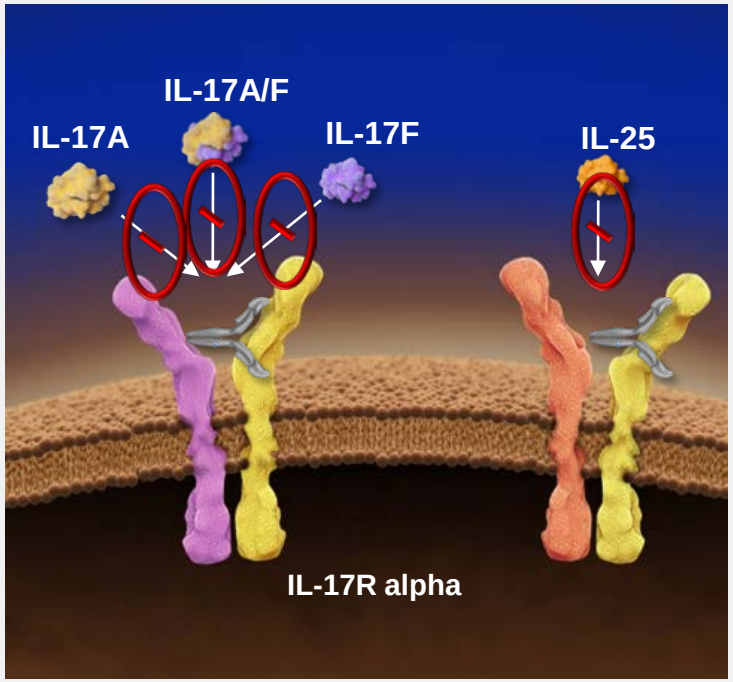


Phase IIb results

- Co-primary endpoints: DAS28, ACR20 highly significant
- Significant benefit after one week
- Significant improvements in patient-reported outcomes
- No apparent safety signals

Source: Clin Pharmacol Ther. 92(3):352-9, 2012

Brodalumab (psoriasis, psoriatic arthritis, asthma): Unique receptor-targeting approach



Targeting IL17 receptor and inhibiting signaling of multiple ligands

Psoriasis

- Three Phase III studies; two with H2H superiority study design vs. Stelara (ustekinumab) and placebo
- First and second Phase III studies achieved primary and secondary endpoints
- Remaining Phase III psoriasis H2H comparator data in Q4 2014

Psoriatic arthritis

- Phase III on track

Asthma

- Opportunity for lifecycle management

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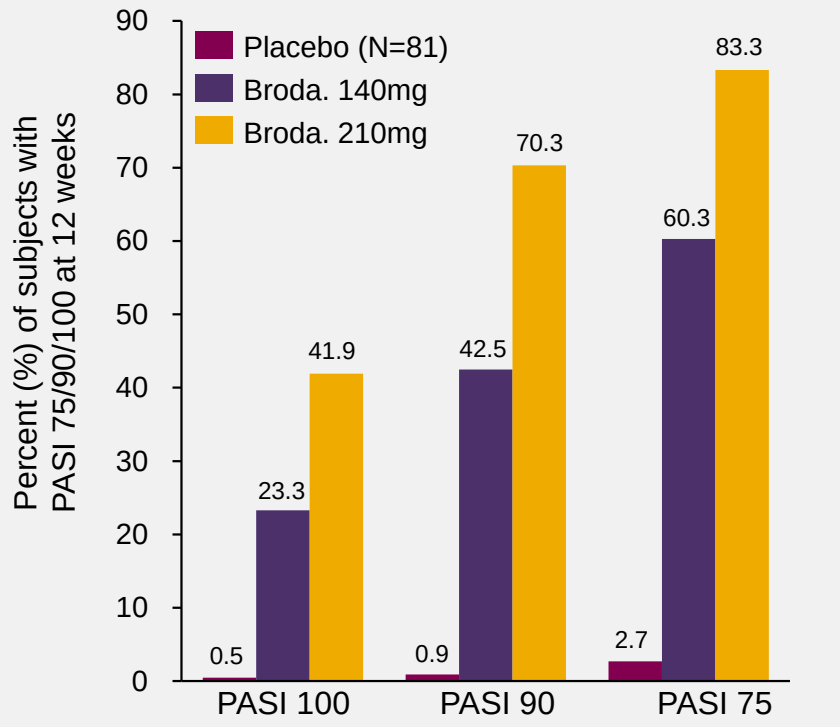
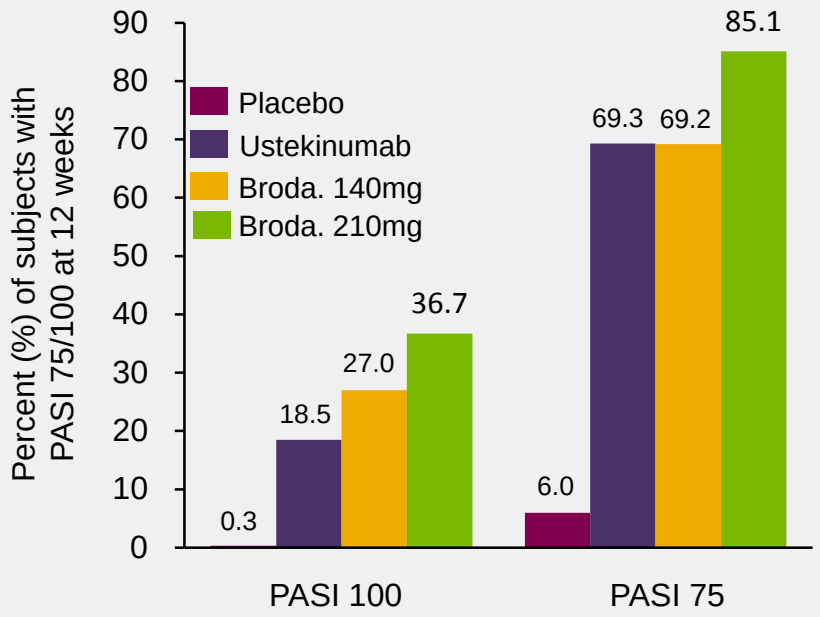
Brodalumab (psoriasis): Positive Phase III data

AMAGINE-1™ Phase III psoriasis data may offer new level of skin clearance



AMAGINE-3™ Phase III H2H ustekinumab comparator



Phase III AMAGINE-2™ H2H comparator study expected in Q4 2014

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Respiratory, Inflammation & Autoimmunity: Lifecycle management of first & best-in-class medicines

Highlighted Phase III and Phase II molecules:

benralizumab	severe asthma	COPD		
tralokinumab	severe asthma	IPF	atopic derm	
brodalumab*	psoriasis	psoriatic arthritis	asthma	
sifalimumab/ anifrolumab	SLE	lupus nephritis	myositis	Sjögren's
MEDI7183*	Crohn's disease	ulcerative colitis		

Lead indication	LCM pursuing now	LCM for future

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2015: Duaklir launch, potential approval, submissions and Phase III starts

Duaklir	**Launch of LAMA-LABA in Genuair device in EU**
lesinurad	**Potential approval of first new MOA for gout in combination with XO**
brodalumab*	**Submission of IL17R for psoriasis**
PT003	**Submission of first pMDI LAMA-LABA**
Phase III starts	**PT010 triple COPD, sifalimumab/anifrolumab, mavrilimumab**

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Summary

Strong respiratory portfolio broadened through Pearl and Almirall

Positive data for first and best-in-class molecules in portfolio

Most comprehensive portfolio of personalised precision therapies

Pipeline: Respiratory, Inflammation & Autoimmunity (RIA)

Inhaled therapeutic leadership; spearheading immunology biologics

Bing Yao, Head of MedImmune Respiratory, Inflammation & Autoimmunity iMED