NOVEL DRUGS

Fibrosing Interstitial Lung Diseases

CPFS/WASOG/AIPO/ERS Conference

Prague, 19-21 June 2014

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Chair of Interstitial Lung Disease
Honorary Consultant Physician

NHS
National Institute for
Health Research

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DISCLOSURES

Scientific Advisory Board

InterMune, Boehringer Ingelheim, Fibrogen, GlaxoSmithKline, Sanofi-Aventis, Anthera, Genentech, Medimmune, Takeda, UCB

Research Grants

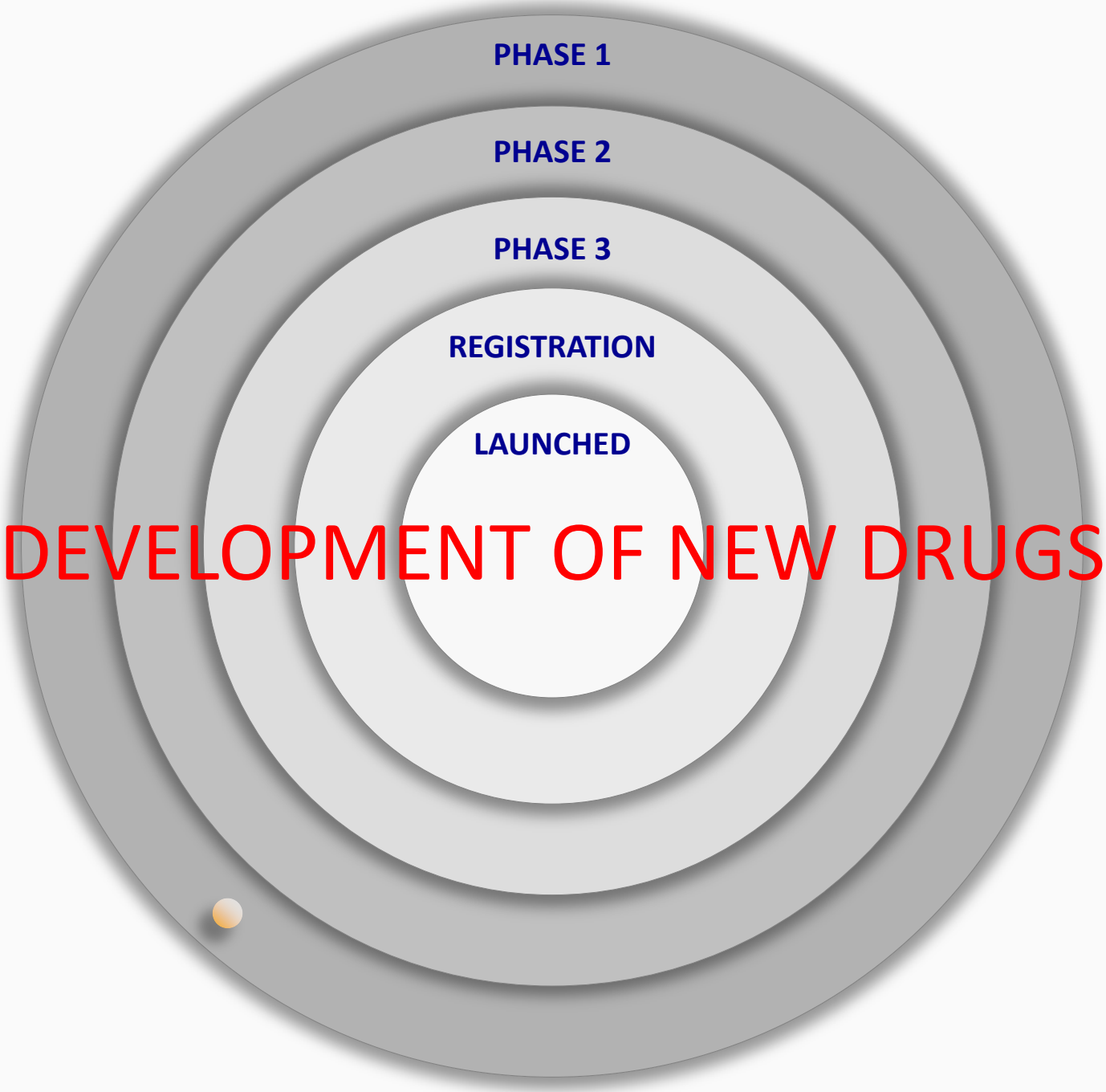
InterMune, Italian Ministry of Health, National Drug Agency (It), National Research Council (It)

Trial Principal Investigator

Boehringer Ingelheim, InterMune, Gilead, Roche, Takeda

Speaker's Fees

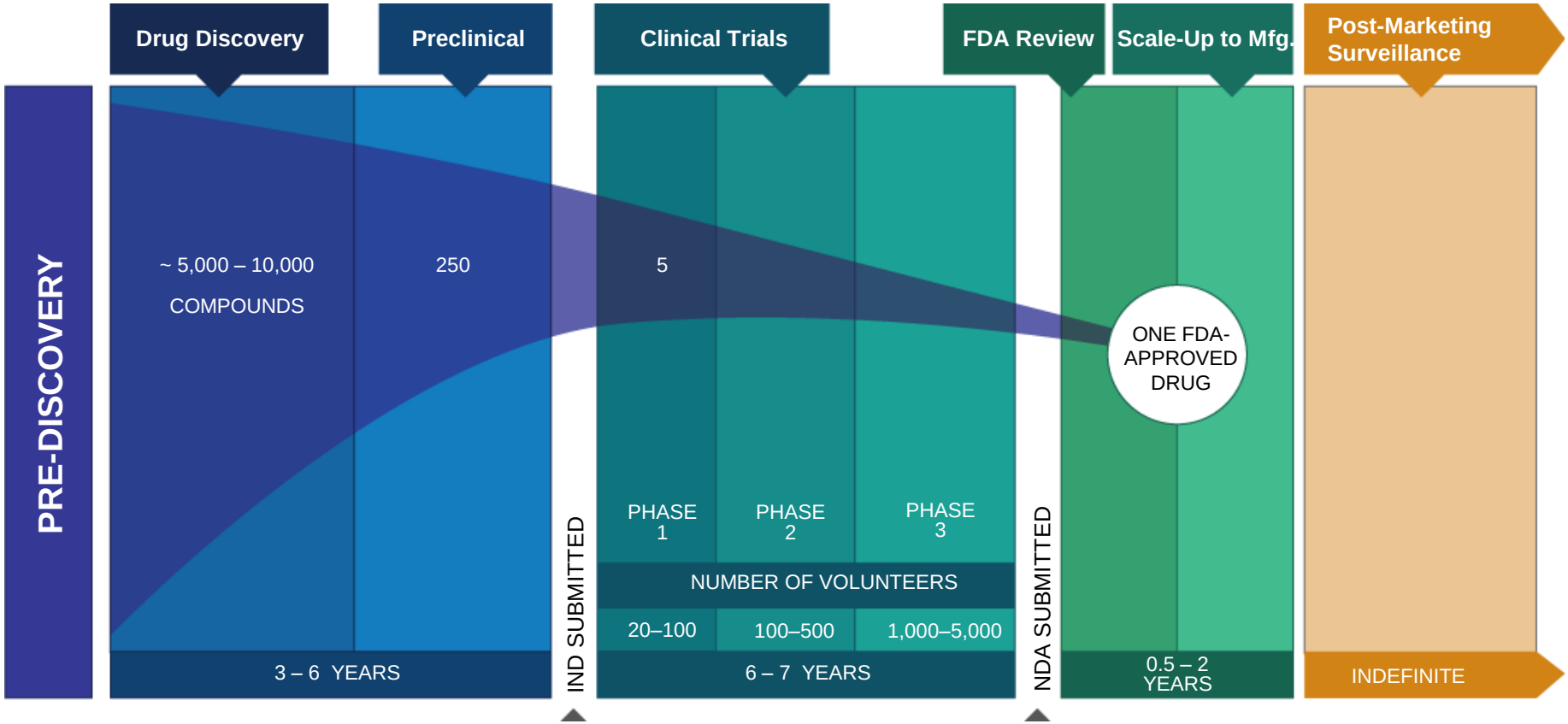
InterMune, Boehringer Ingelheim, Cipla



DEVELOPMENT OF NEW DRUGS

Drug Development Takes Longer Than It Did in the Past

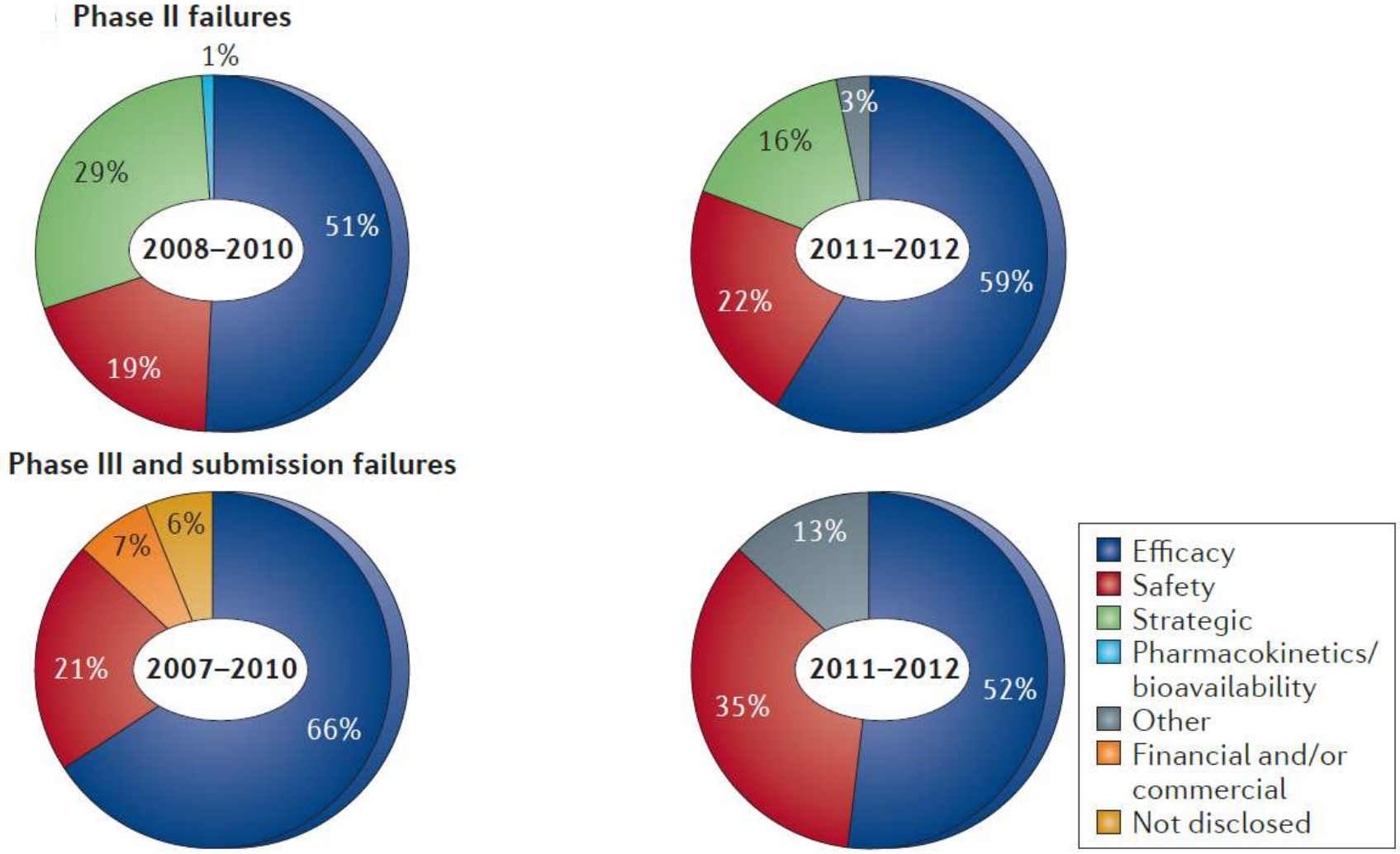
Developing a new medicine takes an average of 10–15 years; the Congressional Budget Office reports that "relatively few drugs survive the clinical trial process"



Sources: Drug Discovery and Development: Understanding the R&D Process, www.innovation.org; CBO, *Research and Development in the Pharmaceutical Industry*, 2006.

innovation.org

REASONS FOR FAILURES IN PHASE II AND PHASE III TRIALS



Arrowsmith J and Miller P, *Nat Rev Drug Discov* 2013; 12: 569

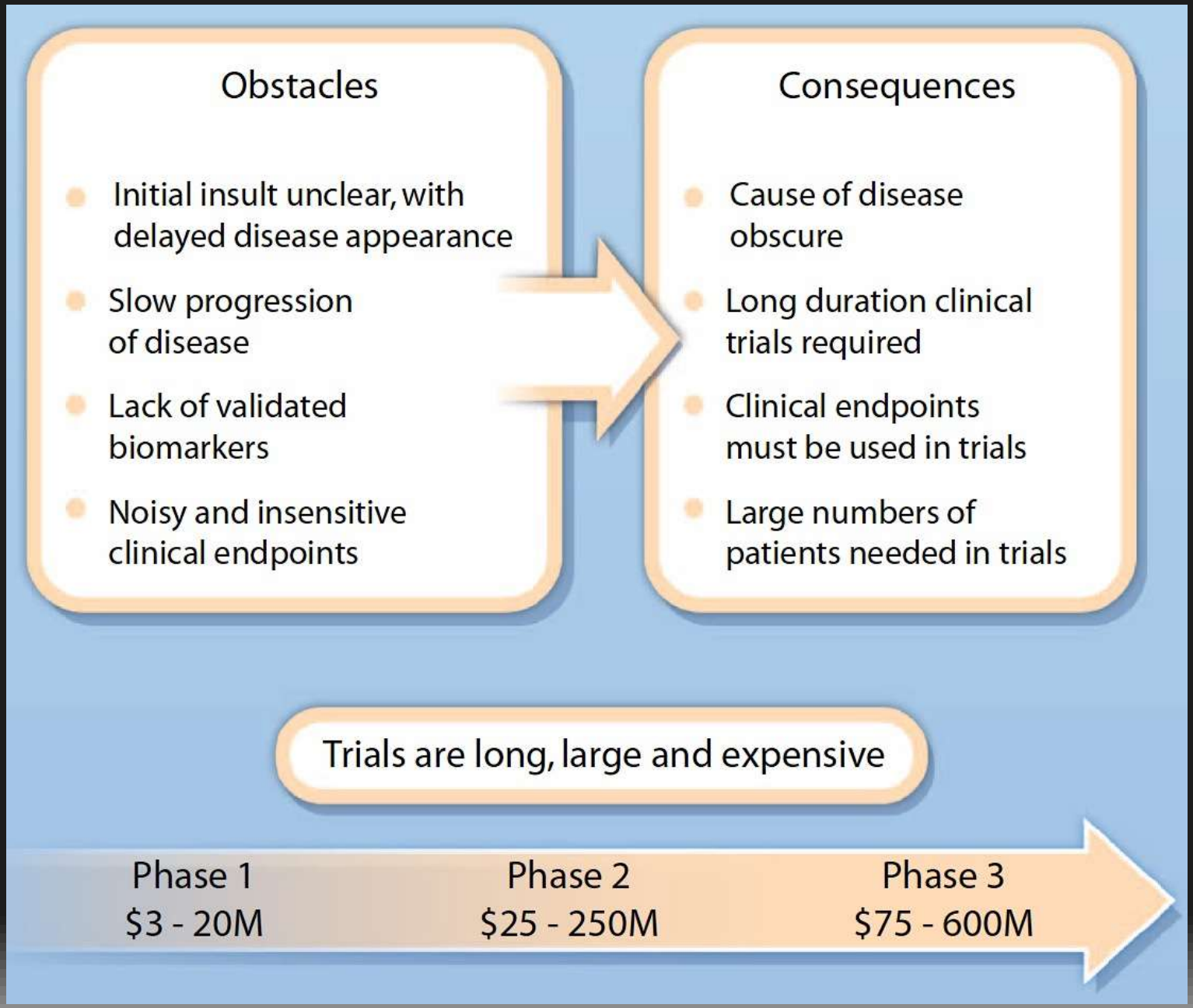
STATE OF THE ART REVIEW

FIBROSIS

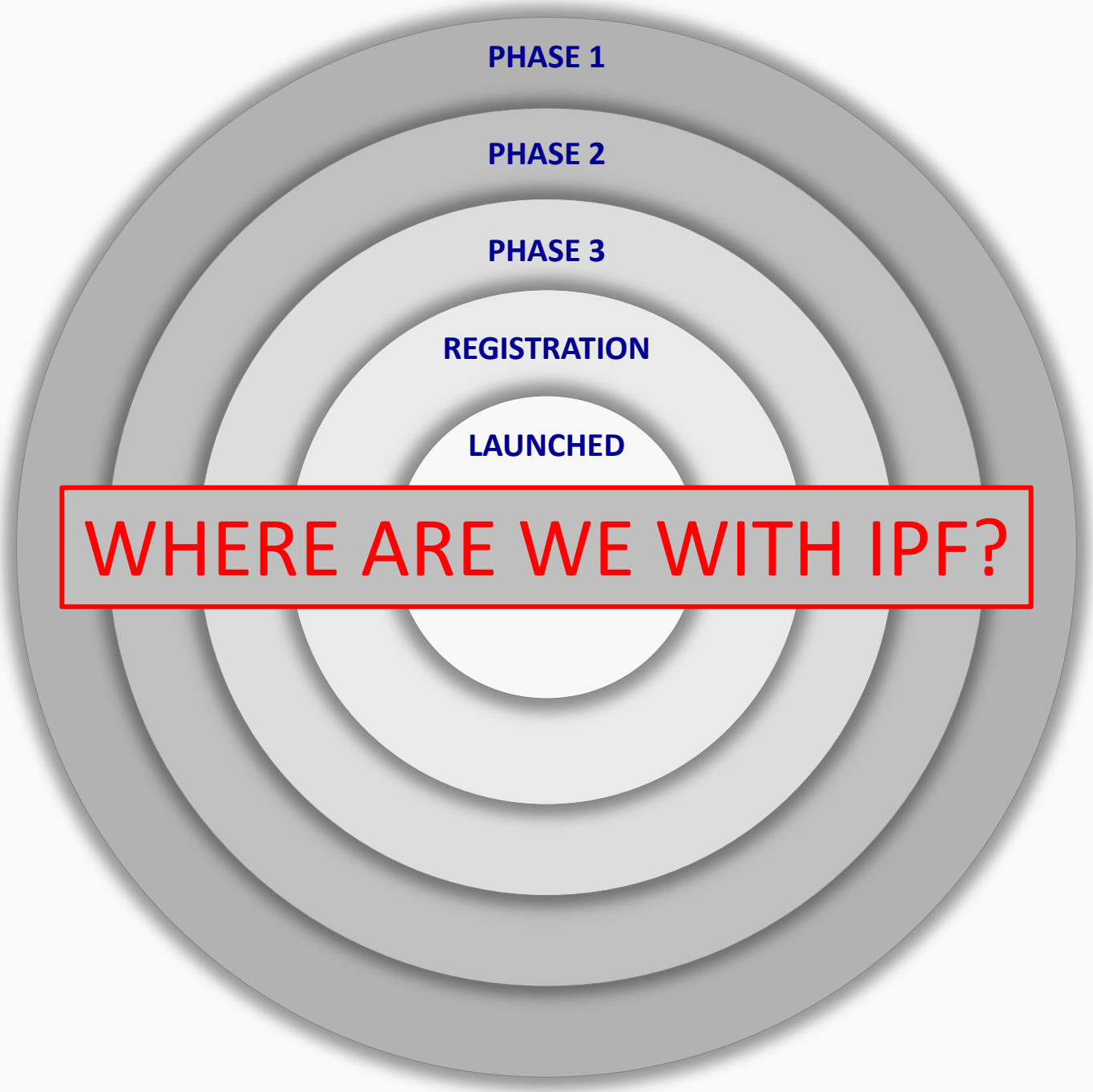
Therapy for Fibrotic Diseases: Nearing the Starting Line

Scott L. Friedman,[1]* Dean Sheppard,[2] Jeremy S. Duffield,[3] Shelia Violette[4]

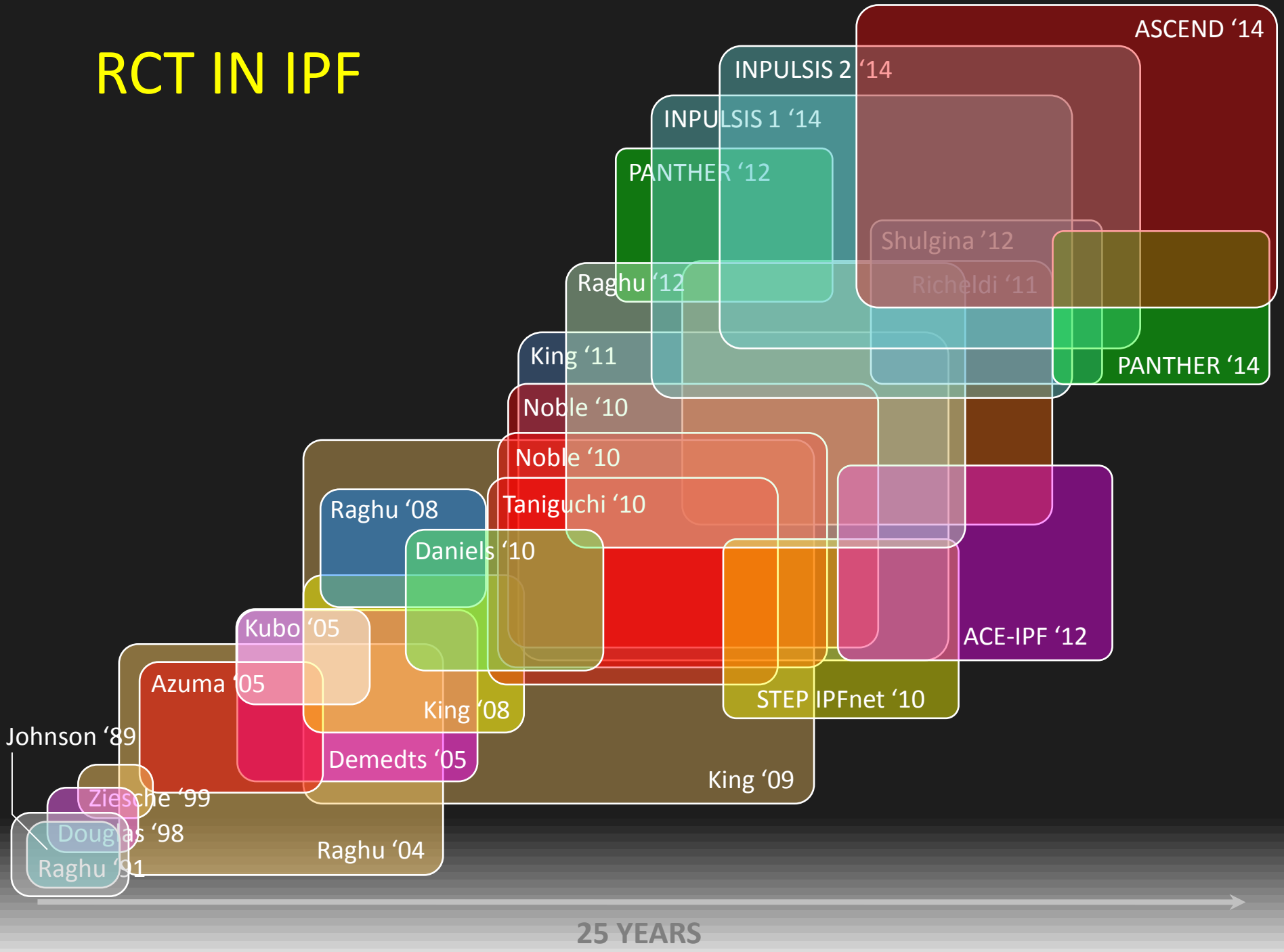
Sci Transl Med 2013; 5: 167sr1. doi: 10.1126/scitranslmed.3004700

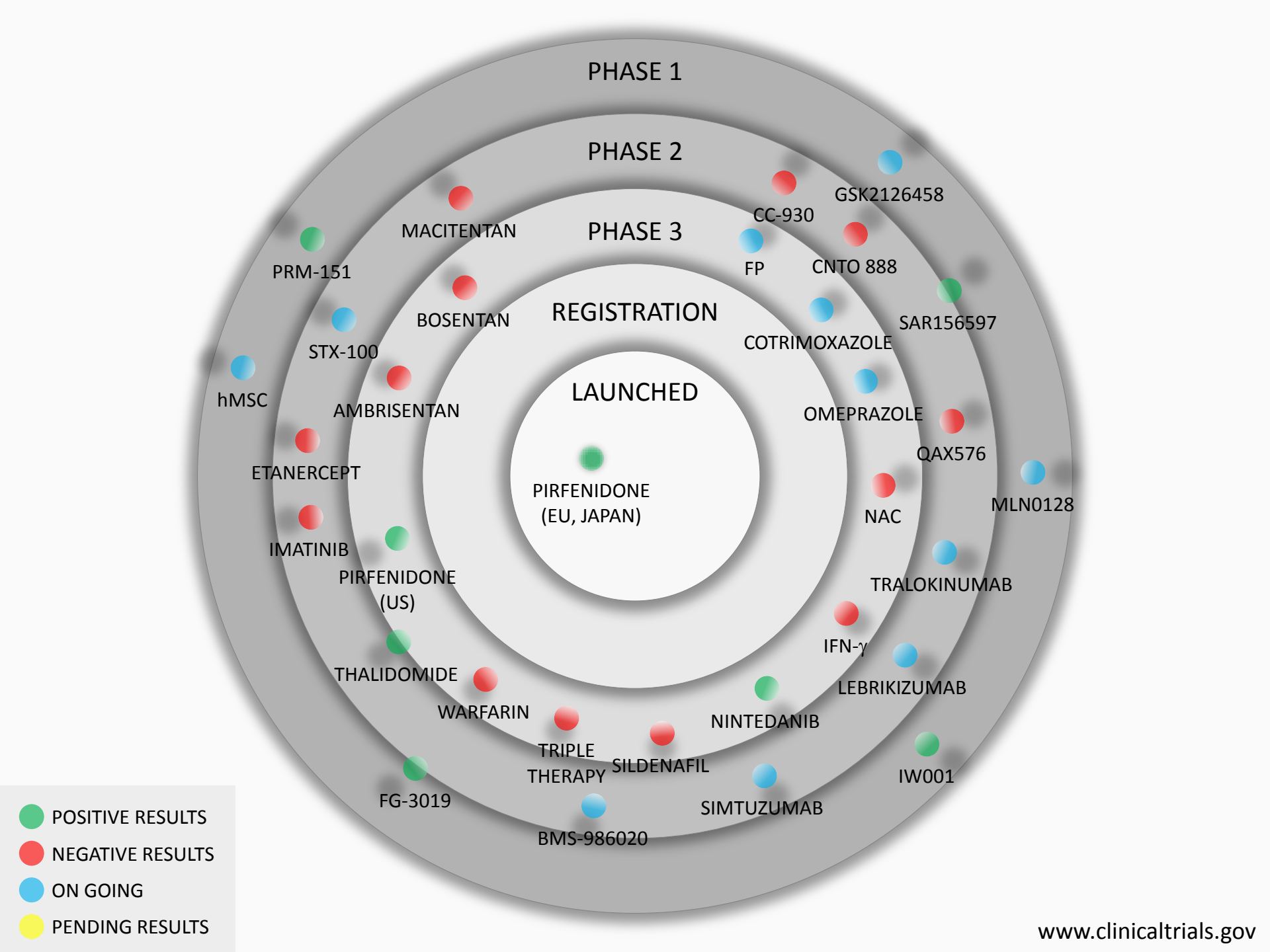


Friedman SL et al, *Sci Transl Med* 2013; 5: 167sr1. doi: 10.1126/scitranslmed.3004700


PHASE 1
PHASE 2
PHASE 3
REGISTRATION
LAUNCHED
WHERE ARE WE WITH IPF?

RCT IN IPF


ASCEND ‘14
INPULSIS 2 ‘14
INPULSIS 1 ‘14
PANTHER ‘12
Shulgina ’12
Richeldi ‘11
Raghu ‘12
PANTHER ‘14
King ‘11
Noble ‘10
Noble ‘10
Raghu ‘08
Taniguchi ‘10
Daniels ‘10
ACE-IPF ‘12
Kubo ‘05
Azuma ‘05
King ‘08
STEP IPFnet ‘10
Johnson ‘89
Demedts ‘05
King ‘09
Ziesche ‘99
Douglas ‘98
Raghu ‘04
Raghu ‘91
25 YEARS


PHASE 1
PHASE 2
PHASE 3
REGISTRATION
LAUNCHED
PIRFENIDONE
(EU, JAPAN)
PRM-151
MACITENTAN
BOSENTAN
STX-100
hMSC
AMBRISENTAN
ETANERCEPT
IMATINIB
PIRFENIDONE
(US)
THALIDOMIDE
WARFARIN
TRIPLE
THERAPY
SILDENAFIL
FG-3019
BMS-986020
SIMTUZUMAB
NINTEDANIB
IFN-γ
LEBRIKIZUMAB
IW001
TRALOKINUMAB
MLN0128
NAC
QAX576
OMEPRAZOLE
COTRIMOXAZOLE
SAR156597
CNTO 888
FP
CC-930
GSK2126458
POSITIVE RESULTS
NEGATIVE RESULTS
ON GOING
PENDING RESULTS
www.clinicaltrials.gov

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

A New Hope for Idiopathic Pulmonary Fibrosis

Gary M. Hunninghake, M.D., M.P.H.

"It is now clear that idiopathic pulmonary fibrosis is a disease perpetuated by aberrant wound healing, rather than primarily by chronic inflammation.

With new understanding comes new hope. As in the 1977 episode of the Star Wars series, the force is finally with us. May we learn to use it wisely."

NEJM 2014; 370: 2142-3

ORIGINAL ARTICLE

A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis

Talmadge E. King, Jr., M.D., Williamson Z. Bradford, M.D., Ph.D., Socorro Castro-Bernardini, M.D., Elizabeth A. Fagan, M.D., Ian Glaspole, M.B., B.S., Ph.D., Marilyn K. Glassberg, M.D., Eduard Gorina, M.D., Peter M. Hopkins, M.D., David Kardatzke, Ph.D., Lisa Lancaster, M.D., David J. Lederer, M.D., Steven D. Nathan, M.D., Carlos A. Pereira, M.D., Steven A. Sahn, M.D., Robert Sussman, M.D., Jeffrey J. Swigris, D.O., and Paul W. Noble, M.D., for the ASCEND Study Group*

ABSTRACT

BACKGROUND

In two of three phase 3 trials, pirfenidone, an oral antifibrotic therapy, reduced disease progression, as measured by the decline in forced vital capacity (FVC) or vital capacity, in patients with idiopathic pulmonary fibrosis; in the third trial, this end point was not achieved. We sought to confirm the beneficial effect of pirfenidone on disease progression in such patients.

METHODS

In this phase 3 study, we randomly assigned 555 patients with idiopathic pulmonary fibrosis to receive either oral pirfenidone (2403 mg per day) or placebo for 52 weeks. The primary end point was the change in FVC or death at week 52. Secondary end points were the 6-minute walk distance, progression-free survival, dyspnea, and death from any cause or from idiopathic pulmonary fibrosis.

RESULTS

In the pirfenidone group, as compared with the placebo group, there was a relative reduction of 47.9% in the proportion of patients who had an absolute decline of 10 percentage points or more in the percentage of the predicted FVC or who died; there was also a relative increase of 132.5% in the proportion of patients with no decline in FVC (P<0.001). Pirfenidone reduced the decline in the 6-minute walk distance (P=0.04) and improved progression-free survival (P<0.001). There was no significant between-group difference in dyspnea scores (P=0.16) or in rates of death from any cause (P=0.10) or from idiopathic pulmonary fibrosis (P=0.23). However, in a prespecified pooled analysis incorporating results from two previous phase 3 trials, the between-group difference favoring pirfenidone was significant for death from any cause (P=0.01) and from idiopathic pulmonary fibrosis (P=0.006). Gastrointestinal and skin-related adverse events were more common in the pirfenidone group than in the placebo group but rarely led to treatment discontinuation.

CONCLUSIONS

Pirfenidone, as compared with placebo, reduced disease progression, as reflected by lung function, exercise tolerance, and progression-free survival, in patients with idiopathic pulmonary fibrosis. Treatment was associated with an acceptable side-effect profile and fewer deaths. (Funded by InterMune; ASCEND ClinicalTrials.gov number, NCT01366209.)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 29, 2014 VOL. 370 NO. 22

Efficacy and Safety of Nintedanib in Idiopathic Pulmonary Fibrosis

Luca Richeldi, M.D., Ph.D., Roland M. du Bois, M.D., Ganesh Raghu, M.D., Arata Azuma, M.D., Ph.D., Kevin K. Brown, M.D., Ulrich Costabel, M.D., Vincent Cottin, M.D., Ph.D., Kevin R. Flaherty, M.D., David M. Hansell, M.D., Yoshikazu Inoue, M.D., Ph.D., Dong Soon Kim, M.D., Martin Kolb, M.D., Ph.D., Andrew G. Nicholson, D.M., Paul W. Noble, M.D., Moisés Selman, M.D., Hiroyuki Taniguchi, M.D., Ph.D., Michèle Brun, M.Sc., Florence Le Maulf, M.Sc., Mannaig Girard, M.Sc., Susanne Stowasser, M.D., Rozsa Schlenker-Herceg, M.D., Bernd Disse, M.D., Ph.D., and Harold R. Collard, M.D., for the INPULSIS Trial Investigators*

ABSTRACT

BACKGROUND

Nintedanib (formerly known as BIBF 1120) is an intracellular inhibitor that targets multiple tyrosine kinases. A phase 2 trial suggested that treatment with 150 mg of nintedanib twice daily reduced lung-function decline and acute exacerbations in patients with idiopathic pulmonary fibrosis.

METHODS

We conducted two replicate 52-week, randomized, double-blind, phase 3 trials (INPULSIS-1 and INPULSIS-2) to evaluate the efficacy and safety of 150 mg of nintedanib twice daily as compared with placebo in patients with idiopathic pulmonary fibrosis. The primary end point was the annual rate of decline in forced vital capacity (FVC). Key secondary end points were the time to the first acute exacerbation and the change from baseline in the total score on the St. George's Respiratory Questionnaire, both assessed over a 52-week period.

RESULTS

A total of 1066 patients were randomly assigned in a 3:2 ratio to receive nintedanib or placebo. The adjusted annual rate of change in FVC was −114.7 ml with nintedanib versus −239.9 ml with placebo (difference, 125.3 ml; 95% confidence interval [CI], 77.7 to 172.8; P<0.001) in INPULSIS-1 and −113.6 ml with nintedanib versus −207.3 ml with placebo (difference, 93.7 ml; 95% CI, 44.8 to 142.7; P<0.001) in INPULSIS-2. In INPULSIS-1, there was no significant difference between the nintedanib and placebo groups in the time to the first acute exacerbation (hazard ratio with nintedanib, 1.15; 95% CI, 0.54 to 2.42; P=0.67); in INPULSIS-2, there was a significant benefit with nintedanib versus placebo (hazard ratio, 0.38; 95% CI, 0.19 to 0.77; P=0.005). The most frequent adverse event in the nintedanib groups was diarrhea, with rates of 61.5% and 18.6% in the nintedanib and placebo groups, respectively, in INPULSIS-1 and 63.2% and 18.3% in the two groups, respectively, in INPULSIS-2.

CONCLUSIONS

In patients with idiopathic pulmonary fibrosis, nintedanib reduced the decline in FVC, which is consistent with a slowing of disease progression; nintedanib was frequently associated with diarrhea, which led to discontinuation of the study medication in less than 5% of patients. (Funded by Boehringer Ingelheim; INPULSIS-1 and INPULSIS-2 ClinicalTrials.gov numbers, NCT01335464 and NCT01335477.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Richeldi at the National Institute for Health Research, Southampton Respiratory Biomedical Research Unit, Mailpoint 813, LF75 E Level, South Academic Block, University Hospital Southampton NHS Foundation Trust, Tremona Rd., Southampton SO16 6YD, United Kingdom, or at l.richeldi@soton.ac.uk.

*A complete list of investigators in the INPULSIS trials is provided in the Supplementary Appendix, available at NEJM.org.

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DOI: 10.1056/NEJMoa1402584

The NEW ENGLAND JOURNAL of MEDICINE

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A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis

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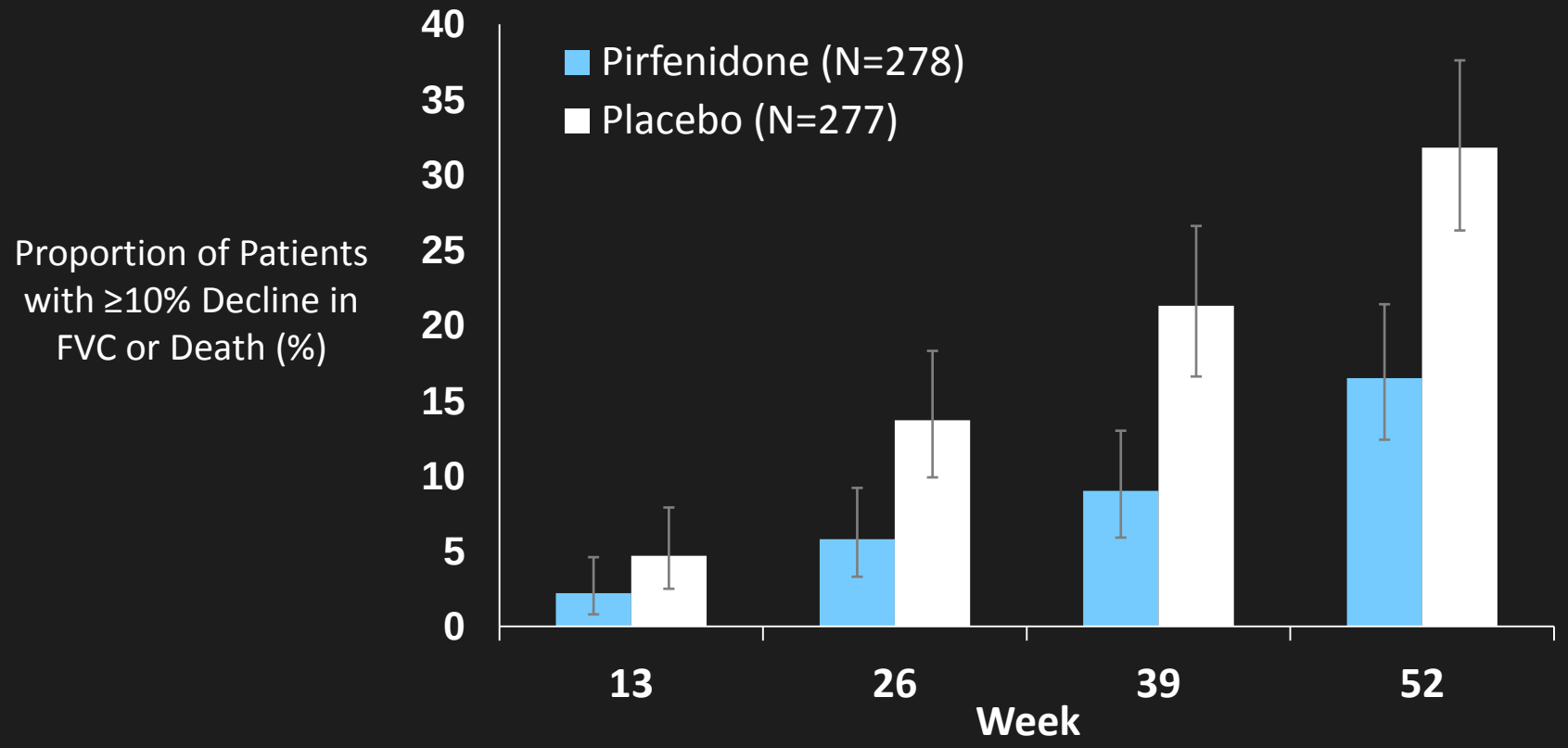
NEJM 2014; 370: 2083-92

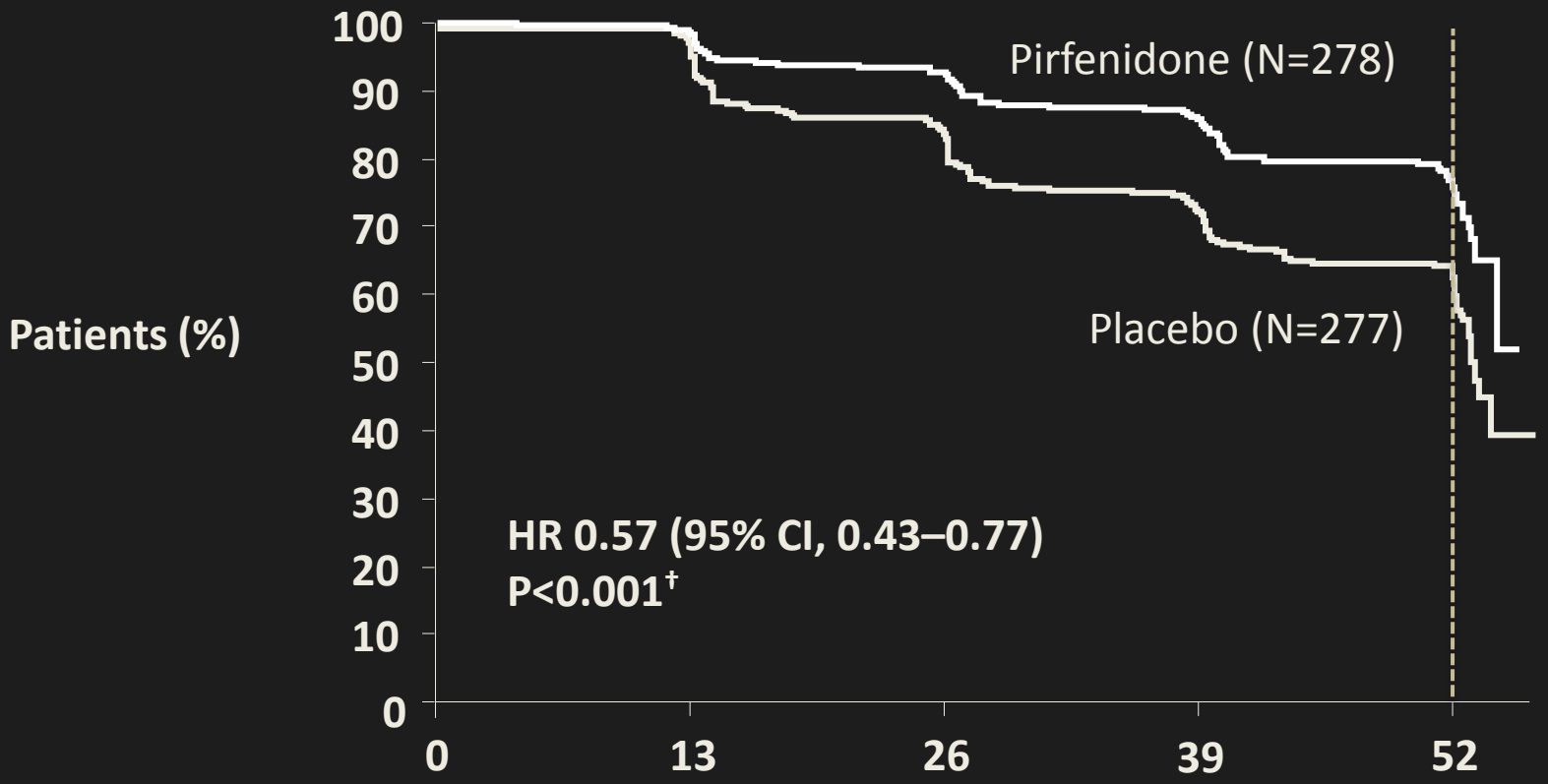
Primary Efficacy Analysis: Treatment with pirfenidone resulted in a significant between-group difference in the rank ANCOVA



Absolute Difference	2.5%	7.9%	12.3%	15.3%
Relative Difference	54.0%	58.0%	57.8%	47.9%
Rank ANCOVA p-value	<0.000001	<0.000001	0.000002	<0.000001

NEJM 2014; 370: 2083-92

Progression-free Survival*: Pirfenidone reduced the risk of disease progression or death by 43%



Patients at Risk:

Pirfenidone	276	262	243	219	144
Placebo	273	269	225	192	113

*Time to death or disease progression (confirmed ≥10% decline in FVC or confirmed ≥50 m decline in 6MWD)

Log-rank test

NEJM 2014; 370: 2083-92

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ESTABLISHED IN 1812 MAY 29, 2014 VOL. 370 NO. 22

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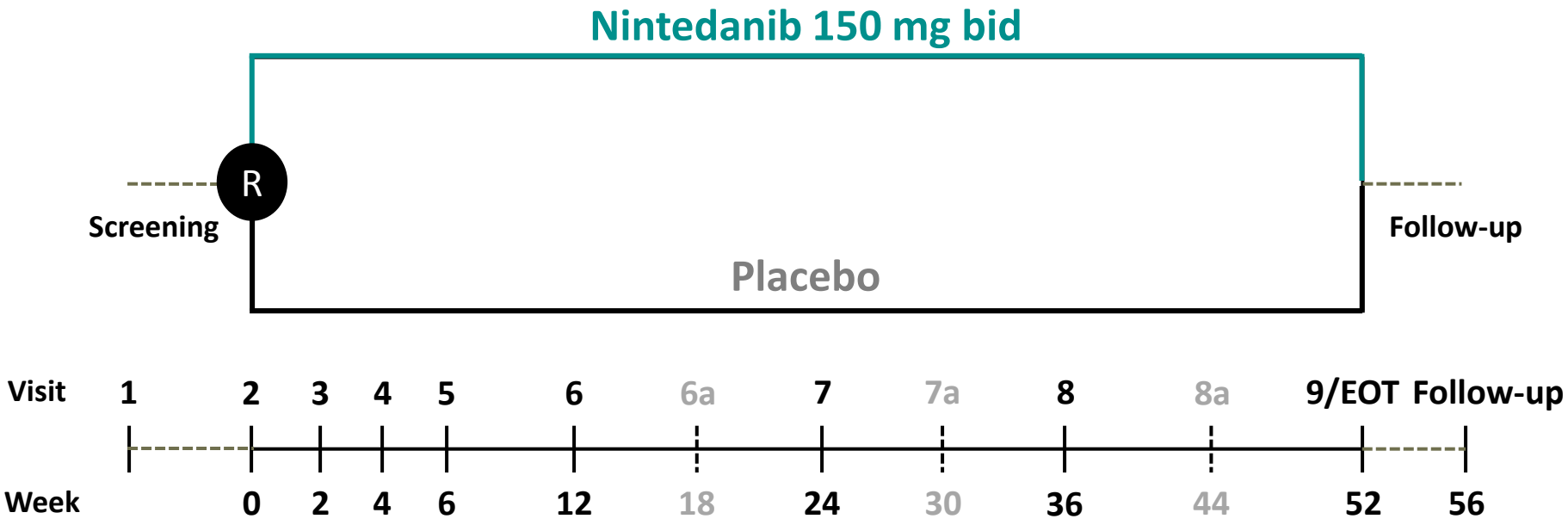
NEJM 2014; 370: 2071-82

STUDY DESIGN

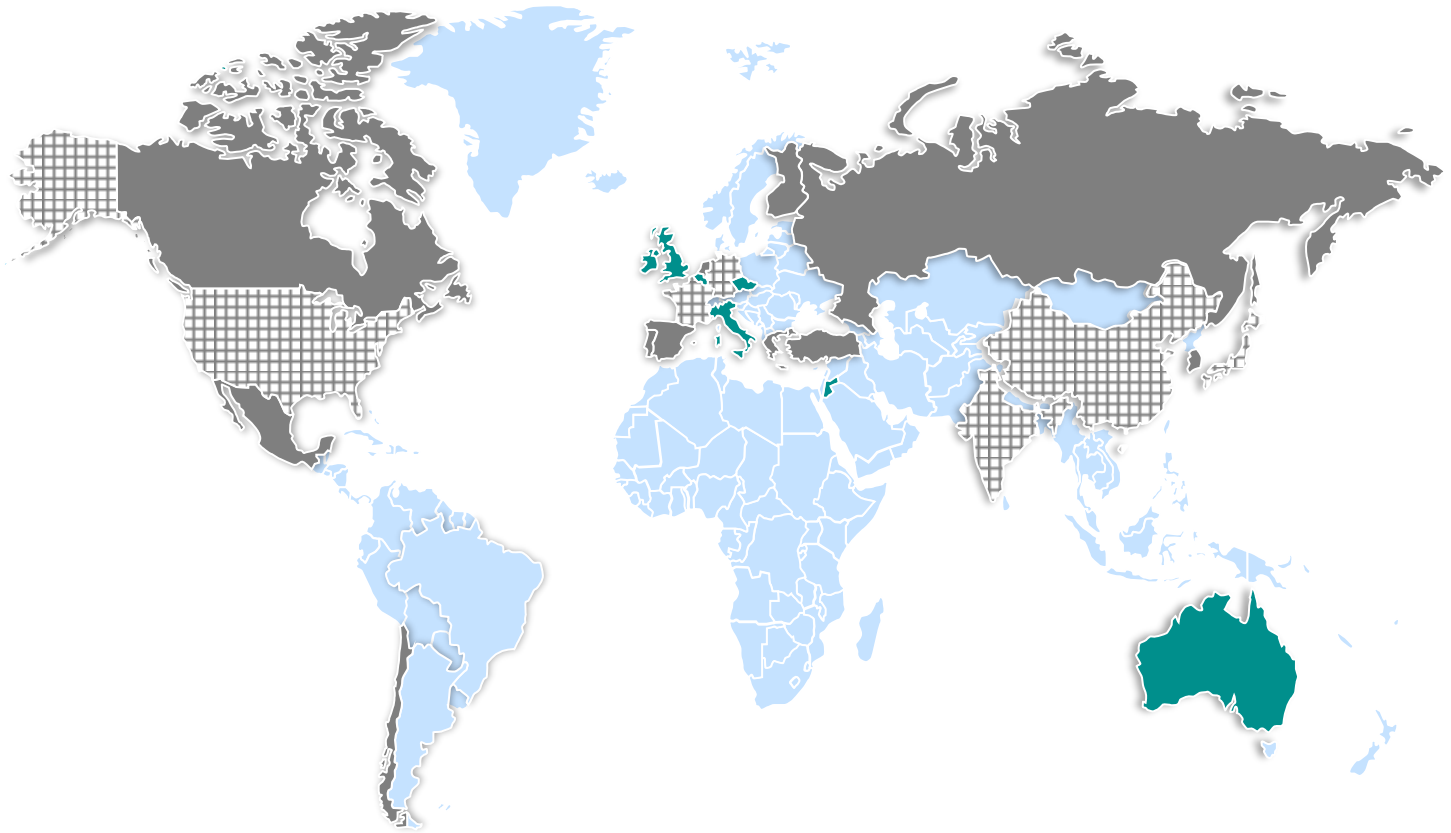


- 3:2 randomization ratio for nintedanib : placebo
- Dose interruption and/or dose reduction to 100 mg bid allowed to manage adverse events
- Patients who prematurely discontinued trial drug were asked to attend all visits as planned

Visits 6a, 7a and 8a were for blood sampling for laboratory tests only

Resp Med 2014; 108: 1023-30

PARTICIPATING COUNTRIES

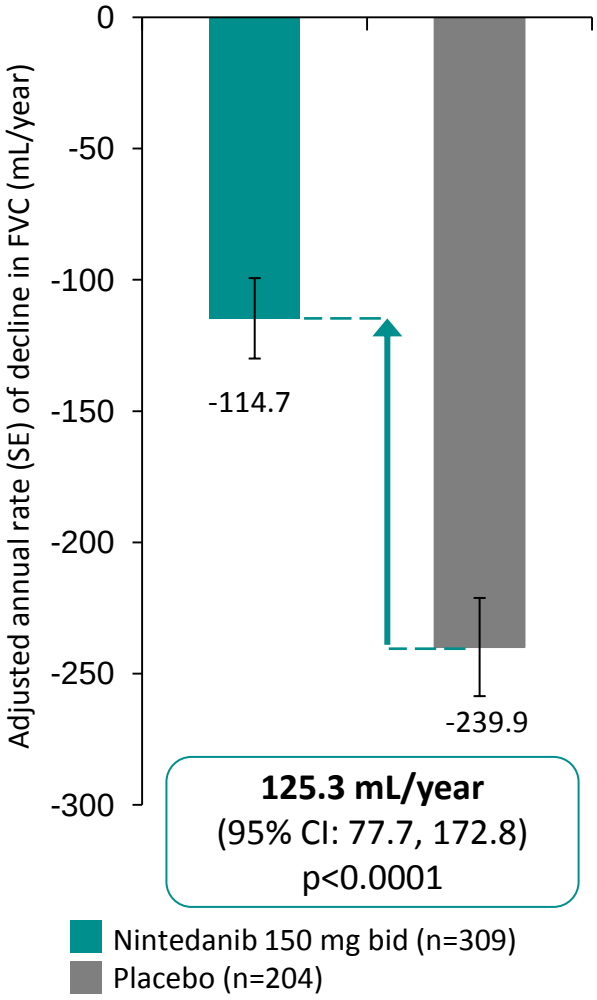


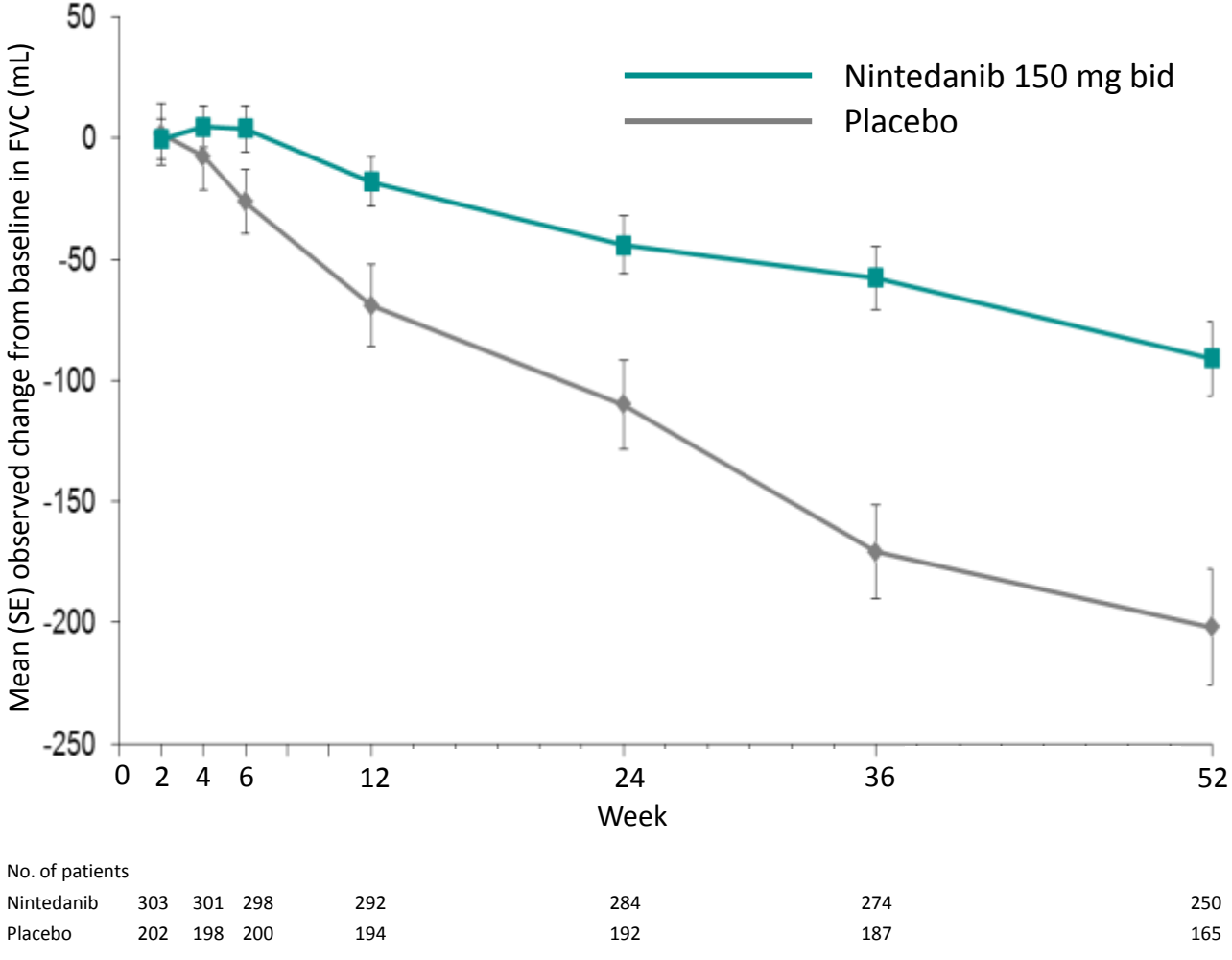
The INPULSIS trials were performed at 205 sites in 24 countries

INPULSIS-1 **INPULSIS-2** **INPULSIS-1 and -2**

Resp Med 2014; 108: 1023-30

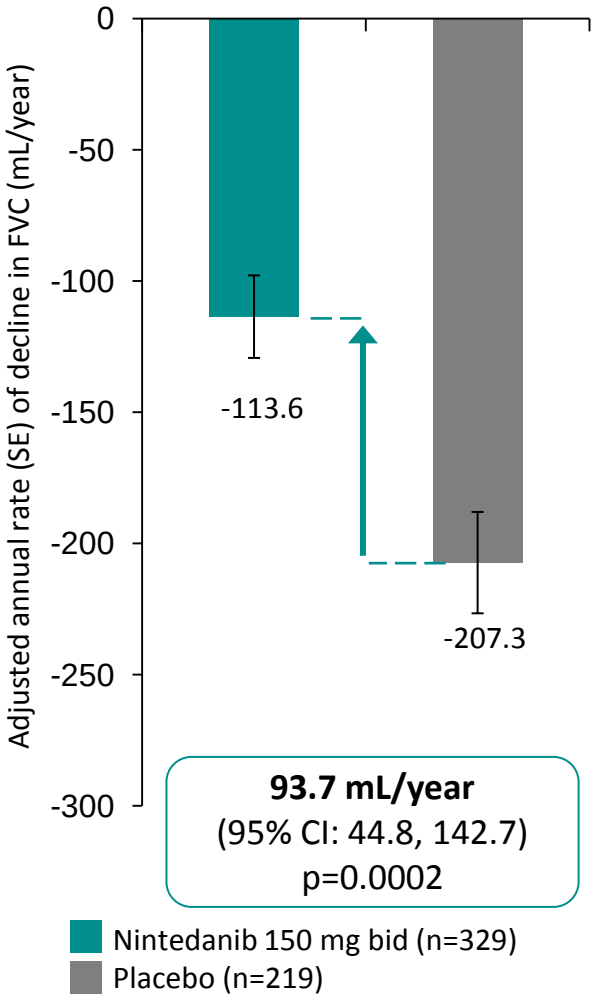
PRIMARY EFFICACY ENDPOINT IN INPULSIS-1

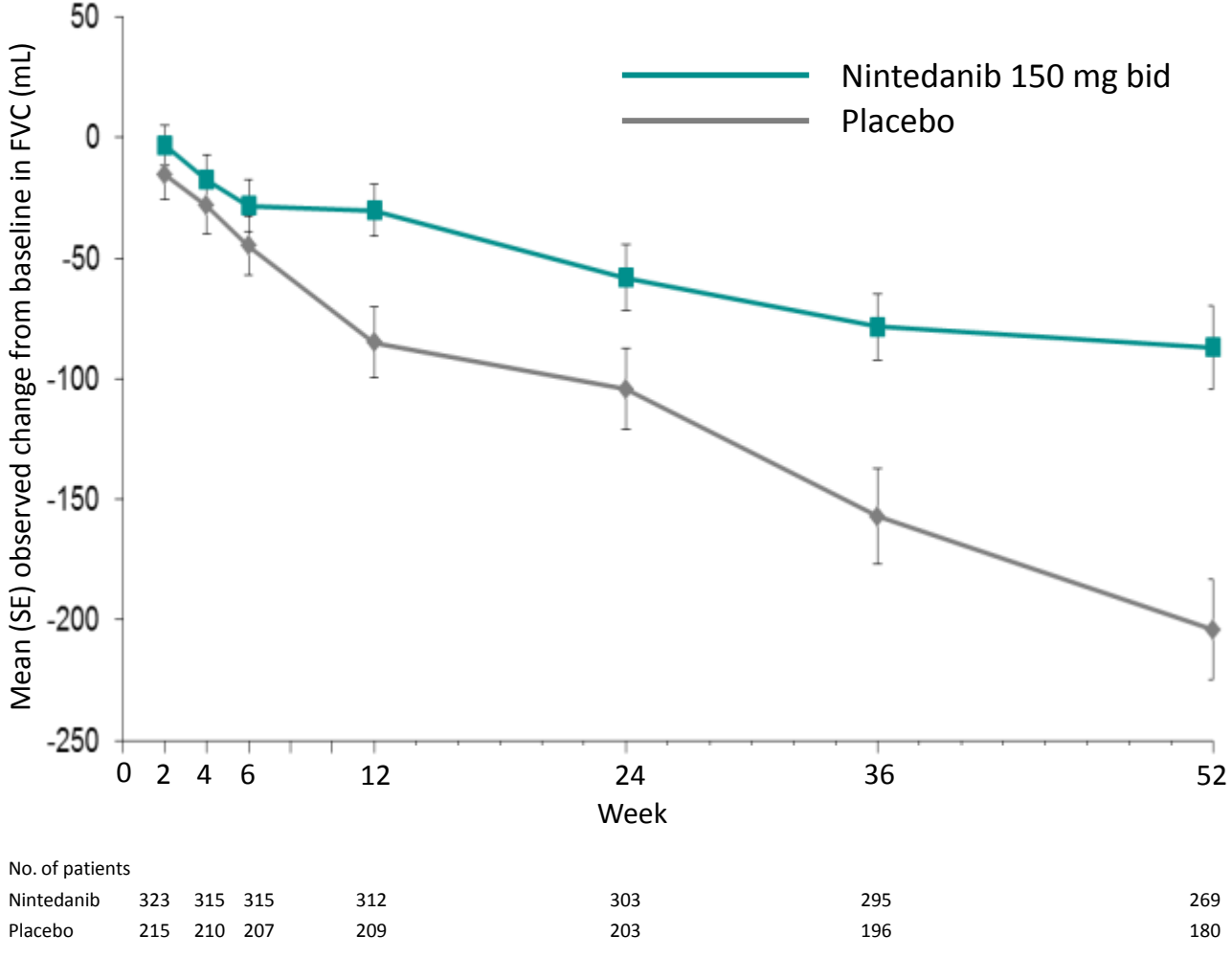




NEJM 2014; 370: 2071-82

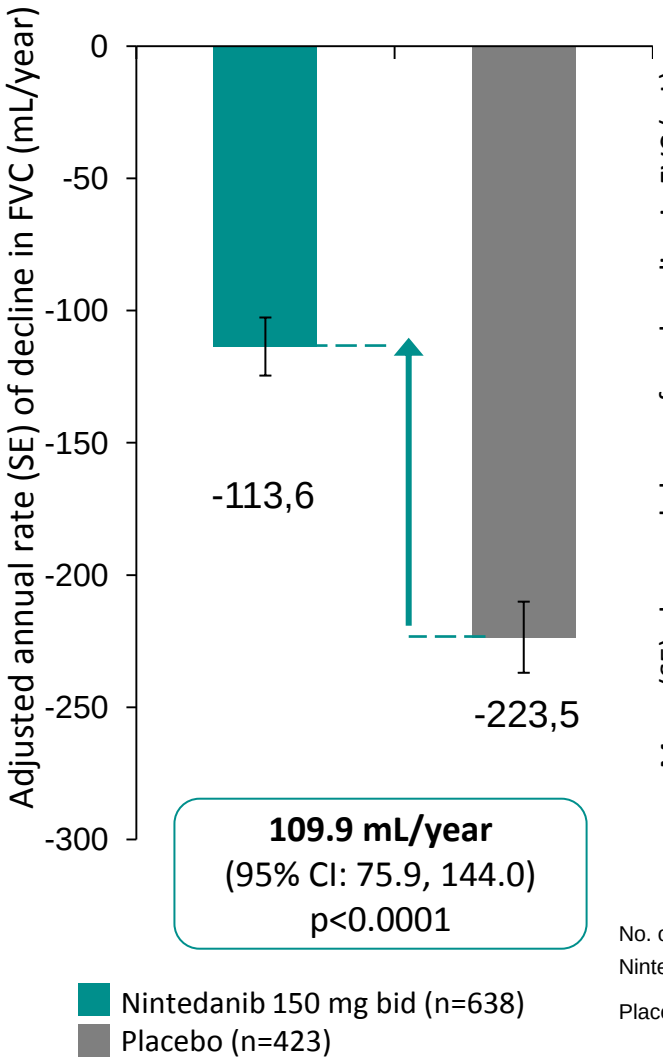
PRIMARY EFFICACY ENDPOINT IN INPULSIS-2

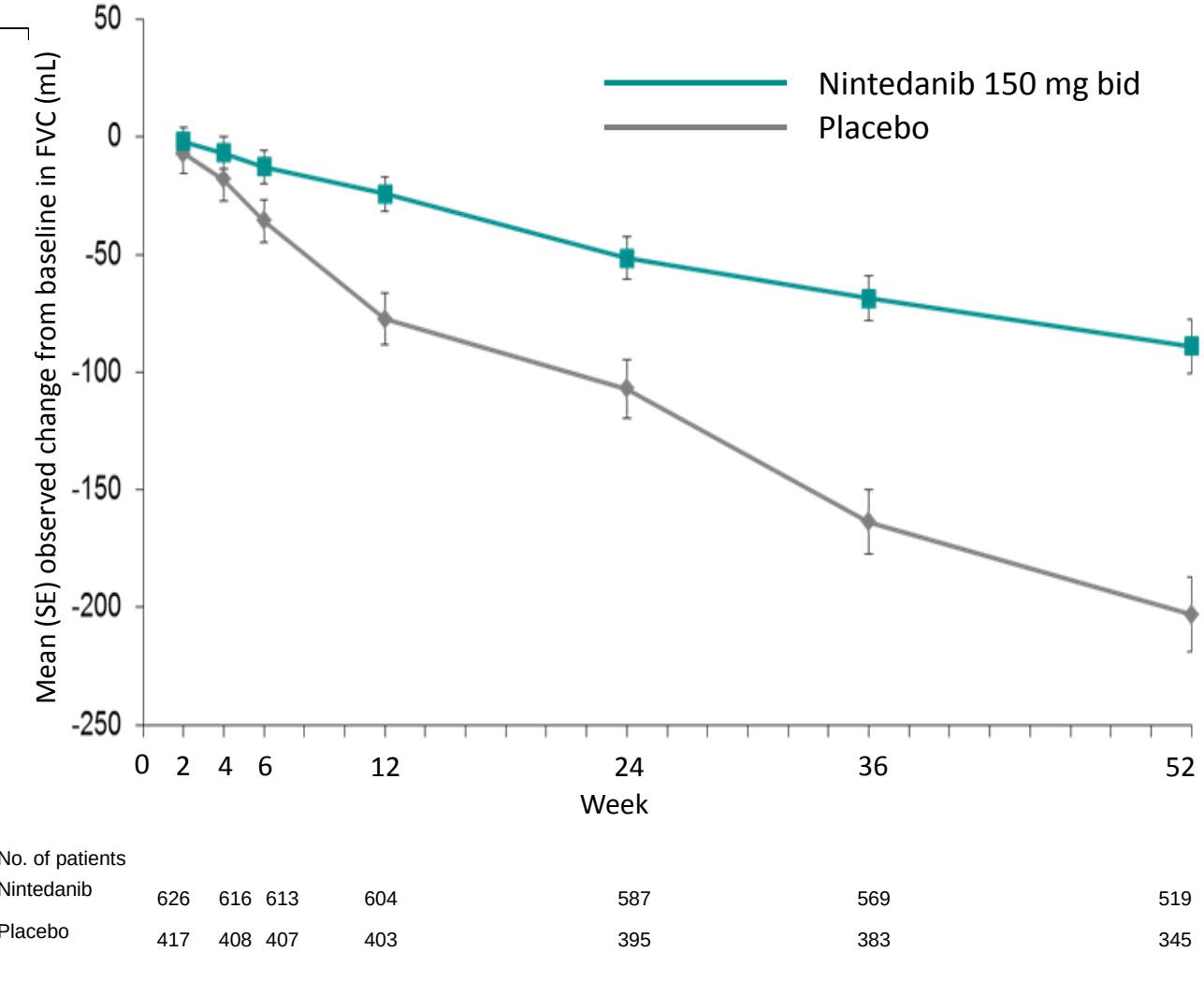




NEJM 2014; 370: 2071-82

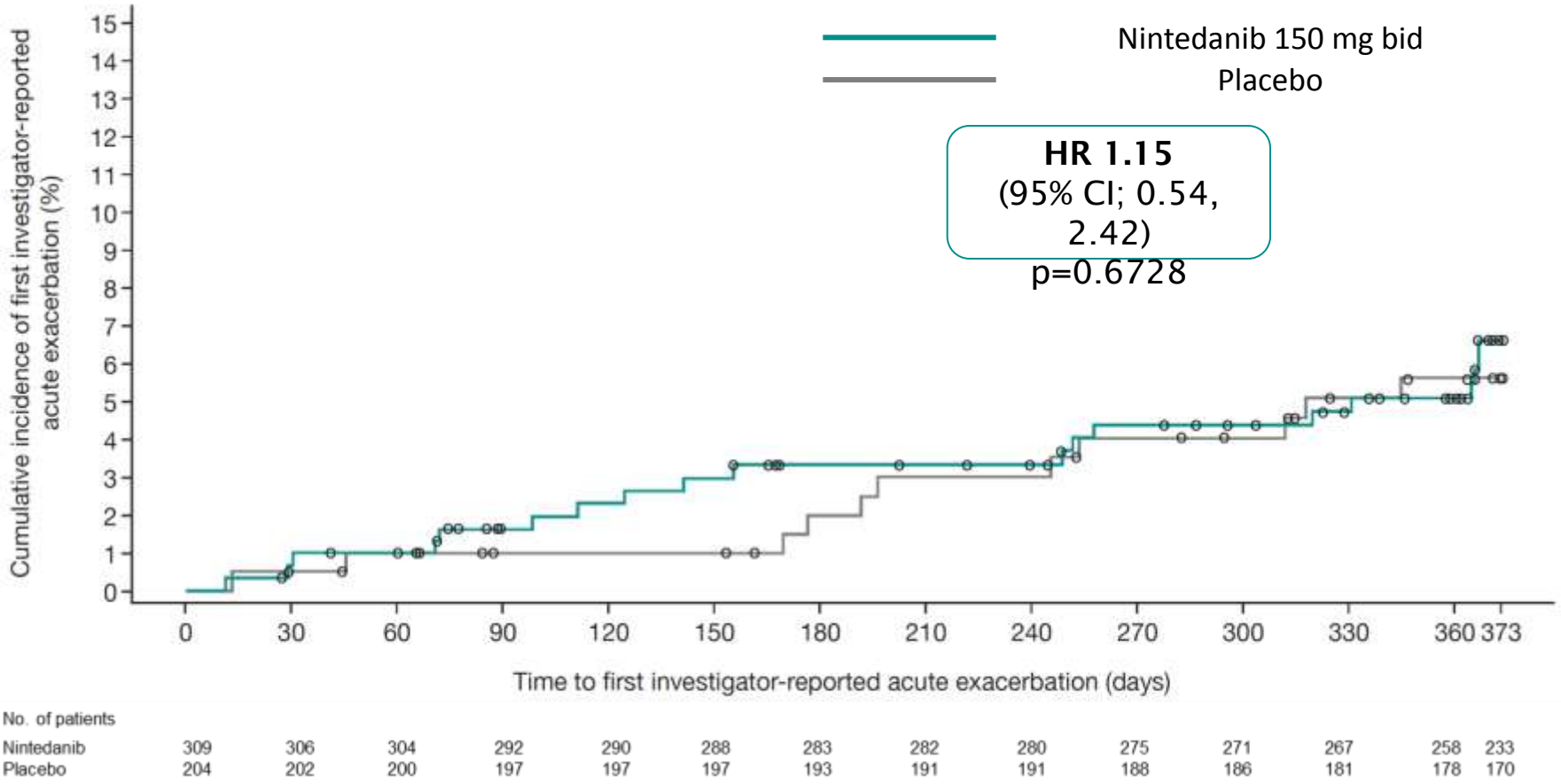
PRIMARY EFFICACY ENDPOINT IN POOLED DATA





NEJM 2014; 370: 2071-82

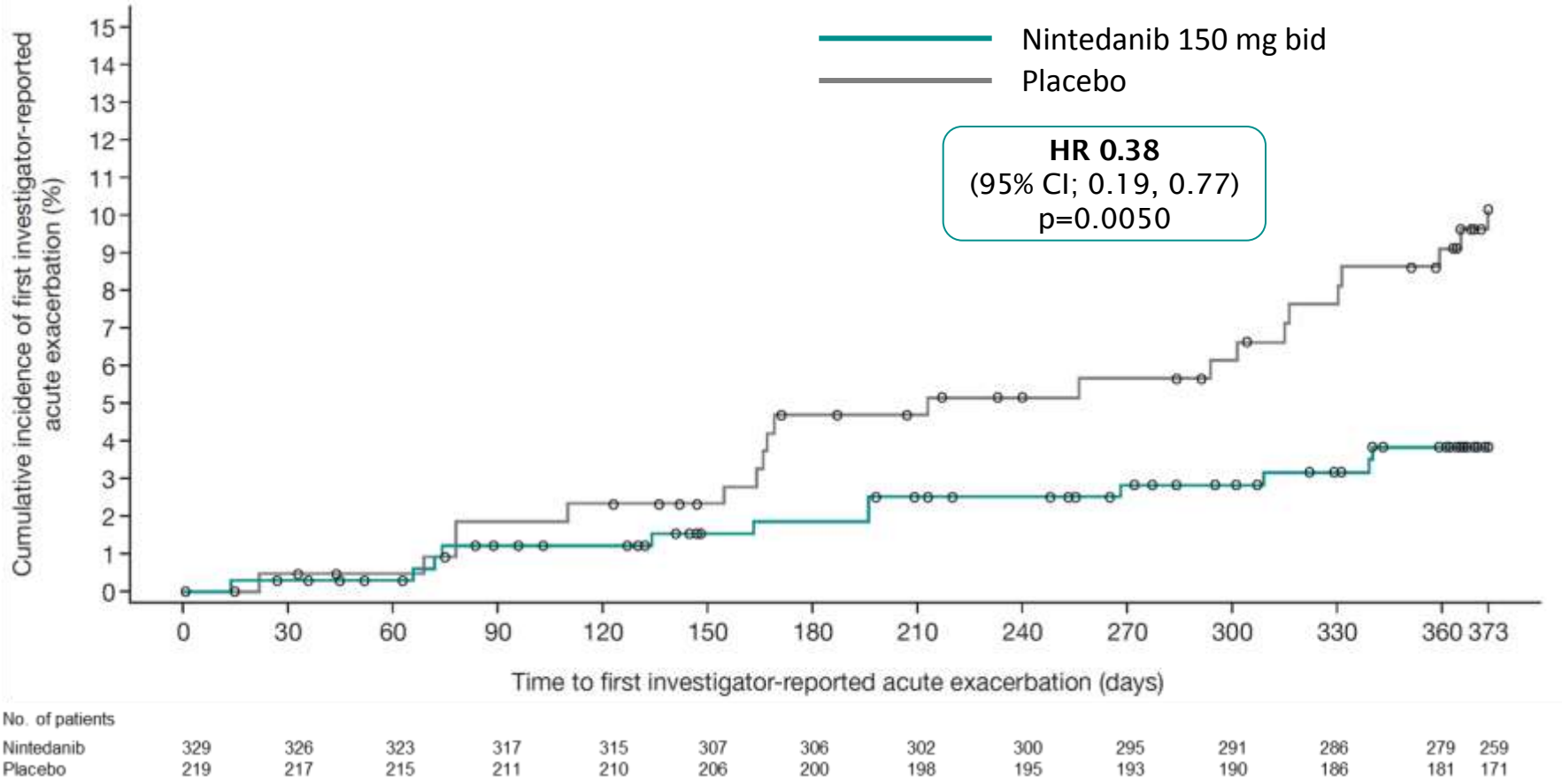
TIME TO FIRST ACUTE EXACERBATION (INVESTIGATOR-REPORTED) IN INPULSIS-1



	Nintedanib 150 mg bid (n=309)	Placebo (n=204)
Patients with ≥1 acute exacerbation, n (%)	19 (6.1)	11 (5.4)

NEJM 2014; 370: 2071-82

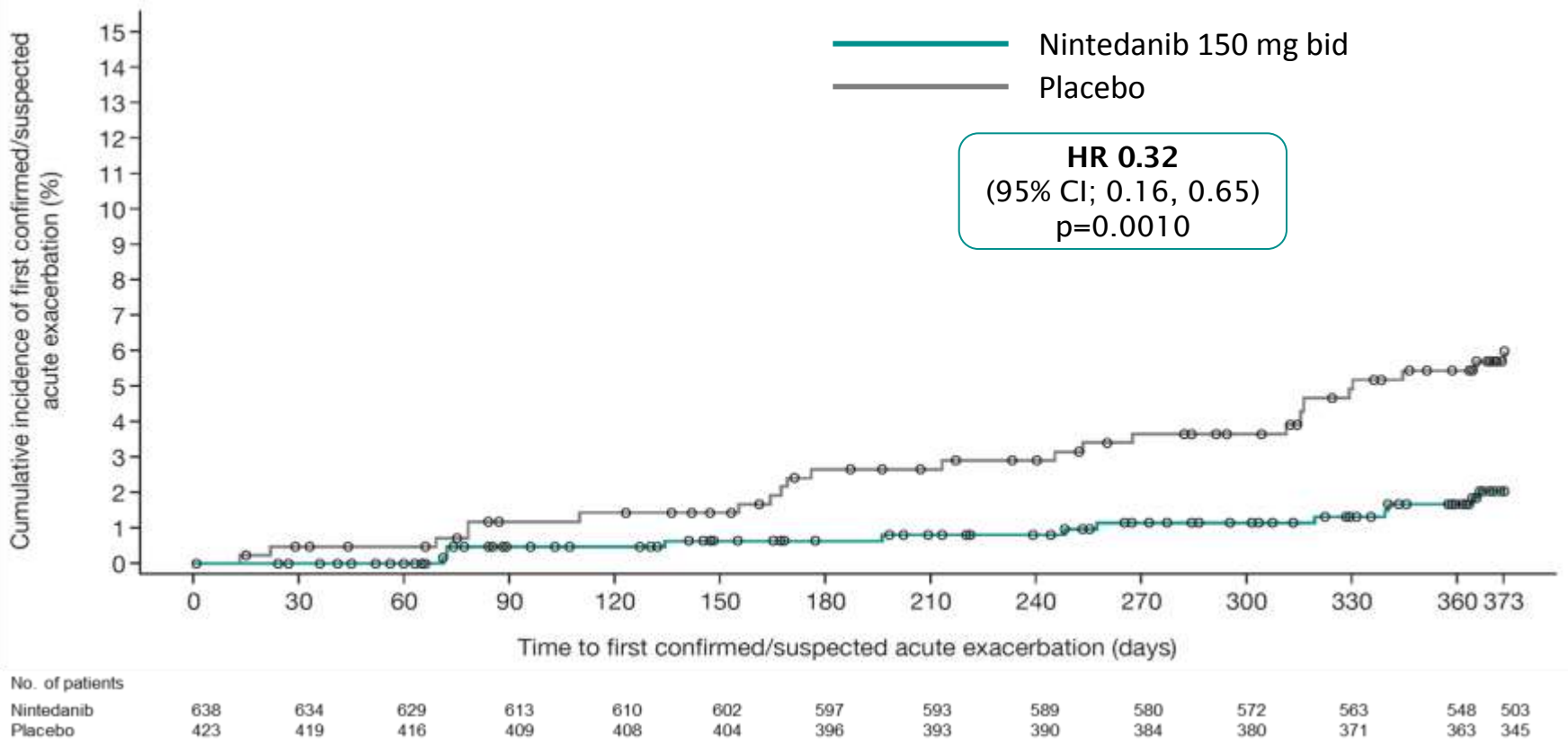
TIME TO FIRST ACUTE EXACERBATION (INVESTIGATOR-REPORTED) IN INPULSIS-2



	Nintedanib 150 mg bid (n=329)	Placebo (n=219)
Patients with ≥1 acute exacerbation, n (%)	12 (3.6)	21 (9.6)

NEJM 2014; 370: 2071-82

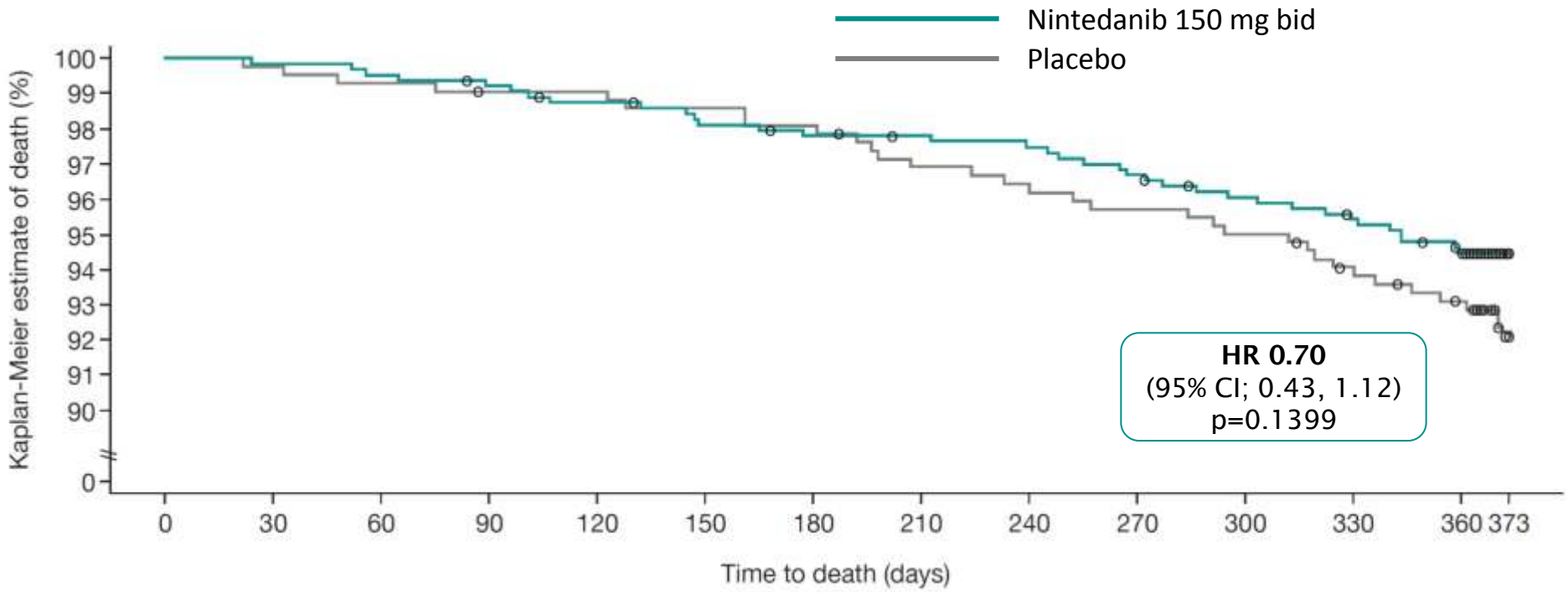
TIME TO FIRST CONFIRMED OR SUSPECTED ACUTE EXACERBATION PER ADJUDICATION (PRESPECIFIED SENSITIVITY ANALYSIS OF POOLED DATA)



	Nintedanib 150 mg bid (n=638)	Placebo (n=423)
Patients with ≥1 acute exacerbation, n (%)	12 (1.9)	24 (5.7)

NEJM 2014; 370: 2071-82

ALL-CAUSE MORTALITY OVER 52 WEEKS (PRESPECIFIED ANALYSIS OF POOLED DATA)



No. of patients														
Nintedanib	638	637	635	632	628	623	620	619	617	612	606	601	591	532
Placebo	423	422	420	418	418	416	414	408	406	403	400	394	388	358

	Nintedanib 150 mg bid (n=638)	Placebo (n=423)
Patients who died, n (%)	35 (5.5)	33 (7.8)

NEJM 2014; 370: 2071-82

MOST FREQUENT ADVERSE EVENTS*

	INPULSIS-1		INPULSIS-2	
No of patients (%)	**Nintedanib 150 mg bid (n=309)**	**Placebo (n=204)**	**Nintedanib 150 mg bid (n=329)**	**Placebo (n=219)**
Diarrhea	190 (61.5)	38 (18.6)	208 (63.2)	40 (18.3)
Nausea	70 (22.7)	12 (5.9)	86 (26.1)	16 (7.3)
Nasopharyngitis	39 (12.6)	34 (16.7)	48 (14.6)	34 (15.5)
Cough	47 (15.2)	26 (12.7)	38 (11.6)	31 (14.2)
Progression of IPF†	31 (10.0)	21 (10.3)	33 (10.0)	40 (18.3)
Bronchitis	36 (11.7)	28 (13.7)	31 (9.4)	17 (7.8)
Upper respiratory tract infection	28 (9.1)	18 (8.8)	30 (9.1)	24 (11.0)
Dyspnea	22 (7.1)	23 (11.3)	27 (8.2)	25 (11.4)
Decreased appetite	26 (8.4)	14 (6.9)	42 (12.8)	10 (4.6)
Vomiting	40 (12.9)	4 (2.0)	34 (10.3)	7 (3.2)
Weight decreased	25 (8.1)	13 (6.4)	37 (11.2)	2 (0.9)

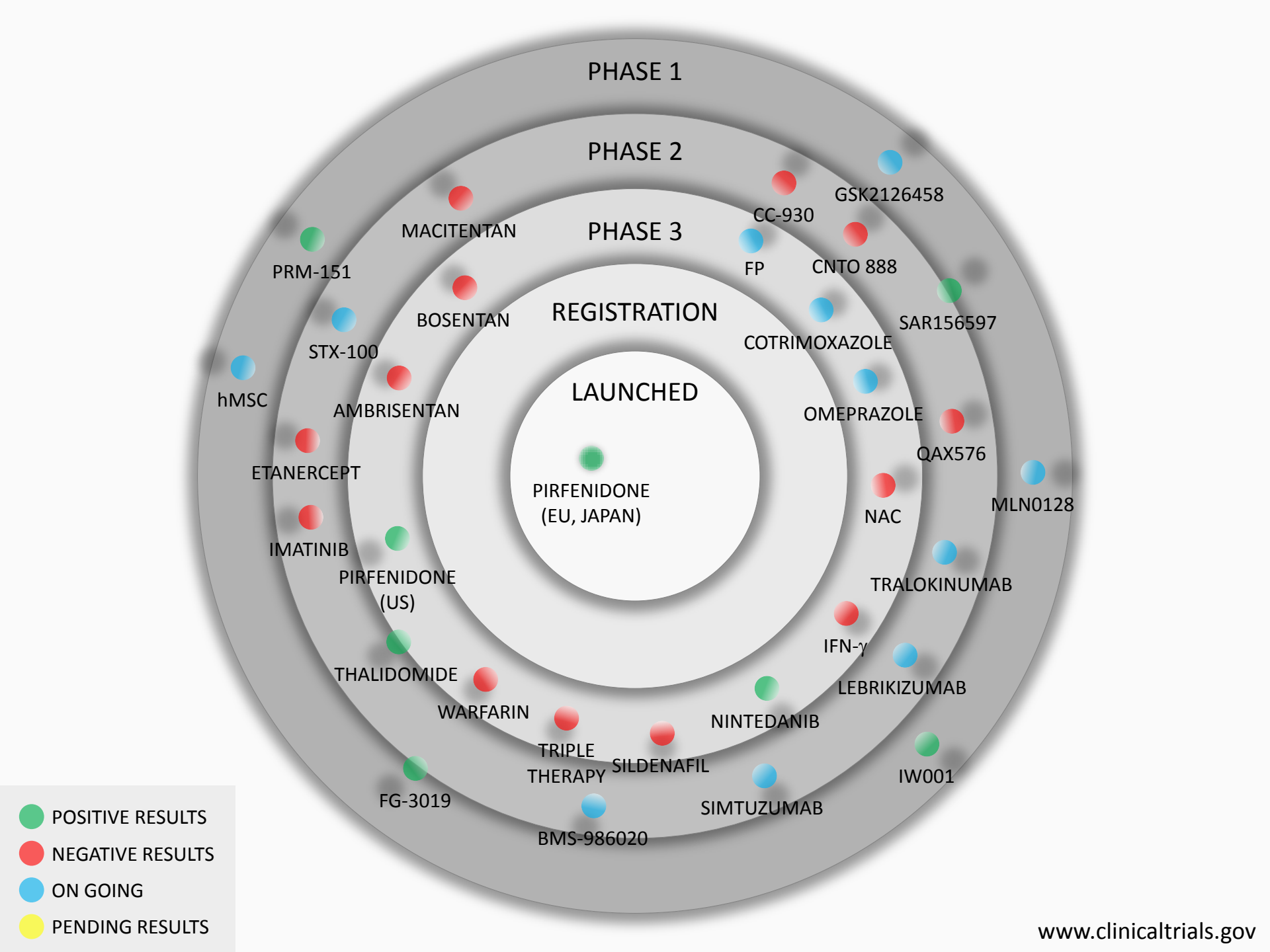
Based on adverse events with onset after first dose and up to 28 days after the last dose of trial medication
*Adverse events with an incidence of >10% in any treatment group. †Corresponds to the MedDRA term 'IPF', which included disease worsening and IPF exacerbations

NEJM 2014; 370: 2071-82

DIARRHEA

	INPULSIS-1		INPULSIS-2	
No of patients (%)	**Nintedanib 150 mg bid (n=309)**	**Placebo (n=204)**	**Nintedanib 150 mg bid (n=329)**	**Placebo (n=219)**
Diarrhea serious adverse event(s)	1 (0.3)	0 (0.0)	1 (0.3)	1 (0.5)
Diarrhea adverse event(s) leading to premature treatment discontinuation	14 (4.5)	0 (0.0)	14 (4.3)	1 (0.5)
Intensity of most severe event, for patients with any diarrhea adverse event(s)				
Mild	103 (54.2)	29 (76.3)	123 (59.1)	31 (77.5)
Moderate	75 (39.5)	9 (23.7)	75 (36.1)	7 (17.5)
Severe	11 (5.8)	0 (0.0)	10 (4.8)	2 (5.0)

NEJM 2014; 370: 2071-82


PHASE 1
PHASE 2
PHASE 3
REGISTRATION
LAUNCHED
PIRFENIDONE
(EU, JAPAN)
PRM-151
MACITENTAN
BOSENTAN
STX-100
hMSC
AMBRISENTAN
ETANERCEPT
IMATINIB
PIRFENIDONE
(US)
THALIDOMIDE
WARFARIN
TRIPLE
THERAPY
SILDENAFIL
FG-3019
BMS-986020
SIMTUZUMAB
NINTEDANIB
IFN-γ
LEBRIKIZUMAB
IW001
TRALOKINUMAB
MLN0128
NAC
QAX576
OMEPRAZOLE
COTRIMOXAZOLE
SAR156597
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CC-930
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POSITIVE RESULTS
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ON GOING
PENDING RESULTS
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EDITORIALS

A New Hope for Idiopathic Pulmonary Fibrosis

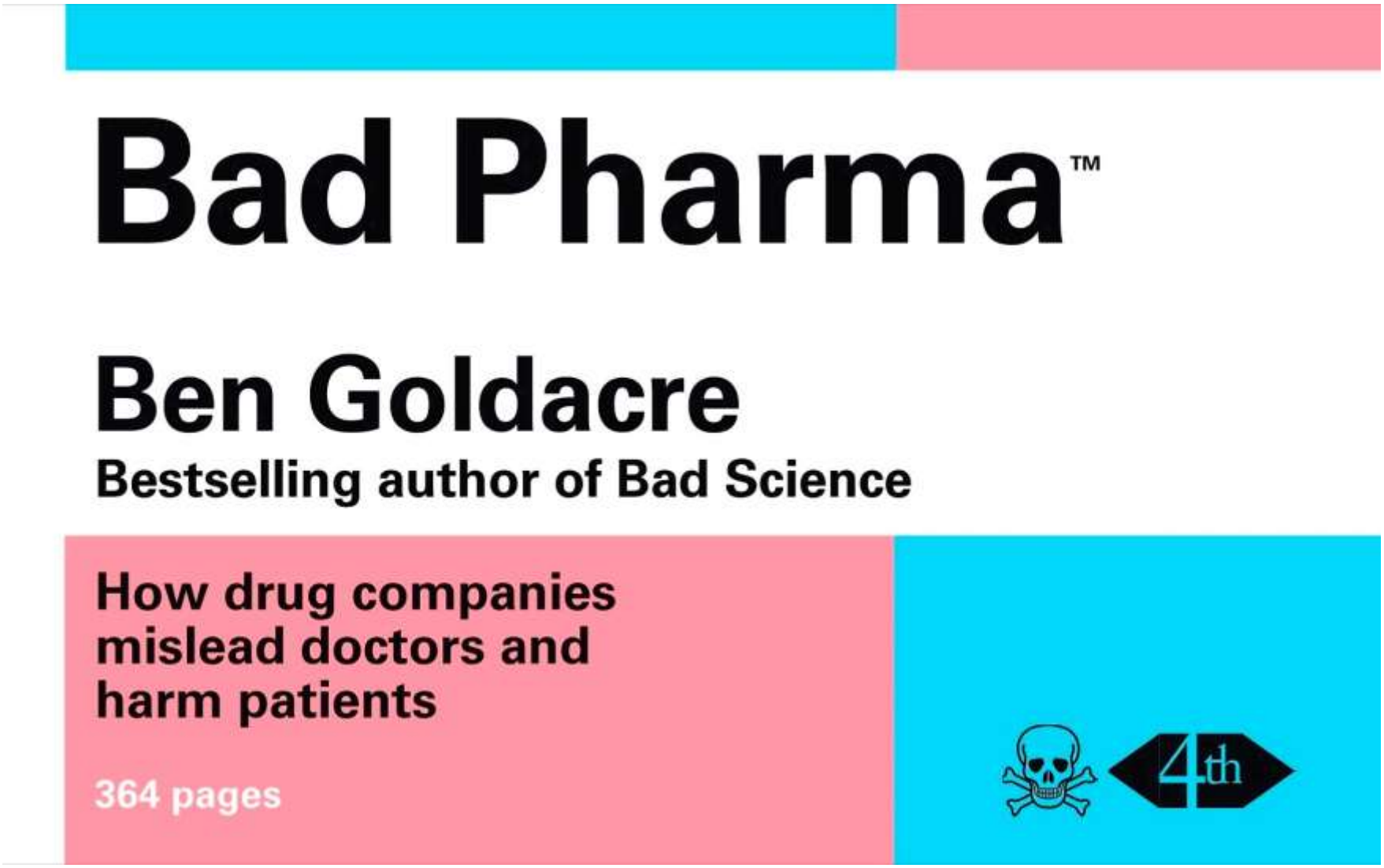
Gary M. Hunninghake, M.D., M.P.H.

"It is now clear that idiopathic pulmonary fibrosis is a disease perpetuated by aberrant wound healing, rather than primarily by chronic inflammation.

With new understanding comes new hope. As in the 1977 episode of the Star Wars series, the force is finally with us. May we learn to use it wisely."

NEJM 2014; 370: 2142-3

DECLINE IN INDUSTRY PHARMACEUTICALS



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- It is based on identifying subgroups of patients with distinct mechanisms of disease, or particular responses to treatments.
- This allows to identify and develop treatments that are effective for particular groups of patients.
- Ultimately stratified medicine will ensure that the right patient gets the right treatment at the right time.
- Stratified medicine has arrived to an extent:
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Towards more precise medicine for the diagnosis, treatment and prevention of disease (iPM)


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Fibrosing Interstitial Lung Diseases

CPFS/WASOG/AIPO/ERS Conference

Prague, 19-21 June 2014

Luca Richeldi MD PhD

Professor of Respiratory Medicine
Chair of Interstitial Lung Disease
Honorary Consultant Physician

NHS
National Institute for
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