Drug Development in Dry AMD: From Target to Therapy

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Disclosures

Novartis – employee

The views expressed in this talk are my own and not those of my employer.

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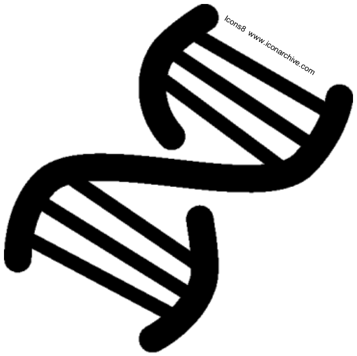
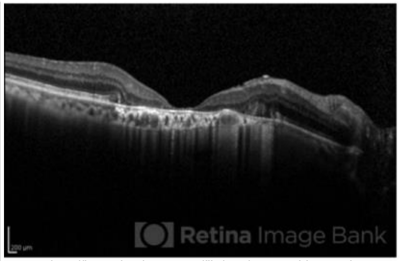
What we know about dry AMD

- **Strongly age-related**

- **Risk factors:**
  - **Genetics**
  - **Smoking**
  - **Environmental/Diet**
  - **others**



- **Slowly progressive**
- **Characteristics:**
  - **Drusen precede late AMD (large confluent >> small)**
  - **Location: macular >> extramacular**
  - **RPE and Photoreceptor loss**



http://imagebank.asrs.org/file/536/geographic-atrophy

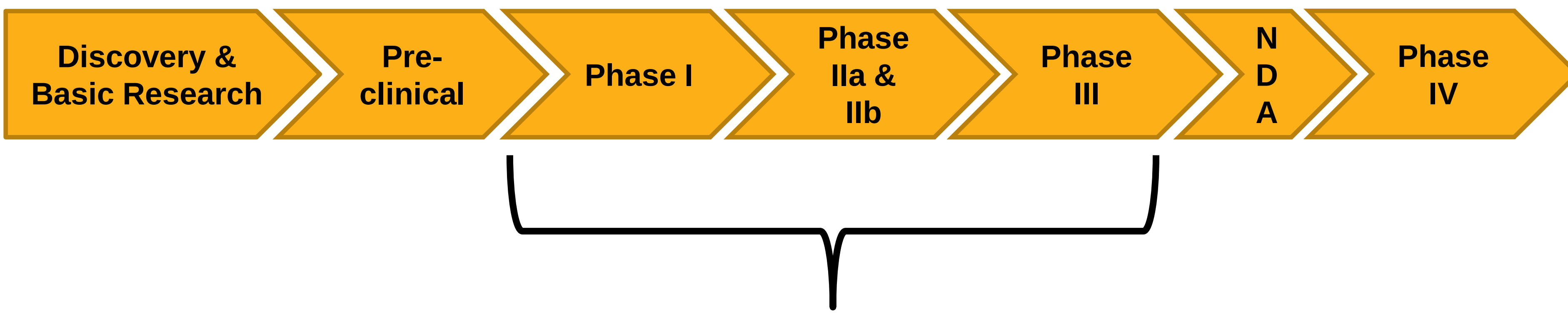
Drug Development in Dry AMD

Unmet Medical Need	✓✓
Target Identification	
Genetics/others	✓
Animal Models	+/-
Biology	+/-
Drugable Targets	✓
Clinical Trial Tractability	+/-

Path from Target to Drug

Staged Development

Traditional drug development



Traditional Clinical Drug Development

Compound ready now (3 month endpoint): ~8+ years

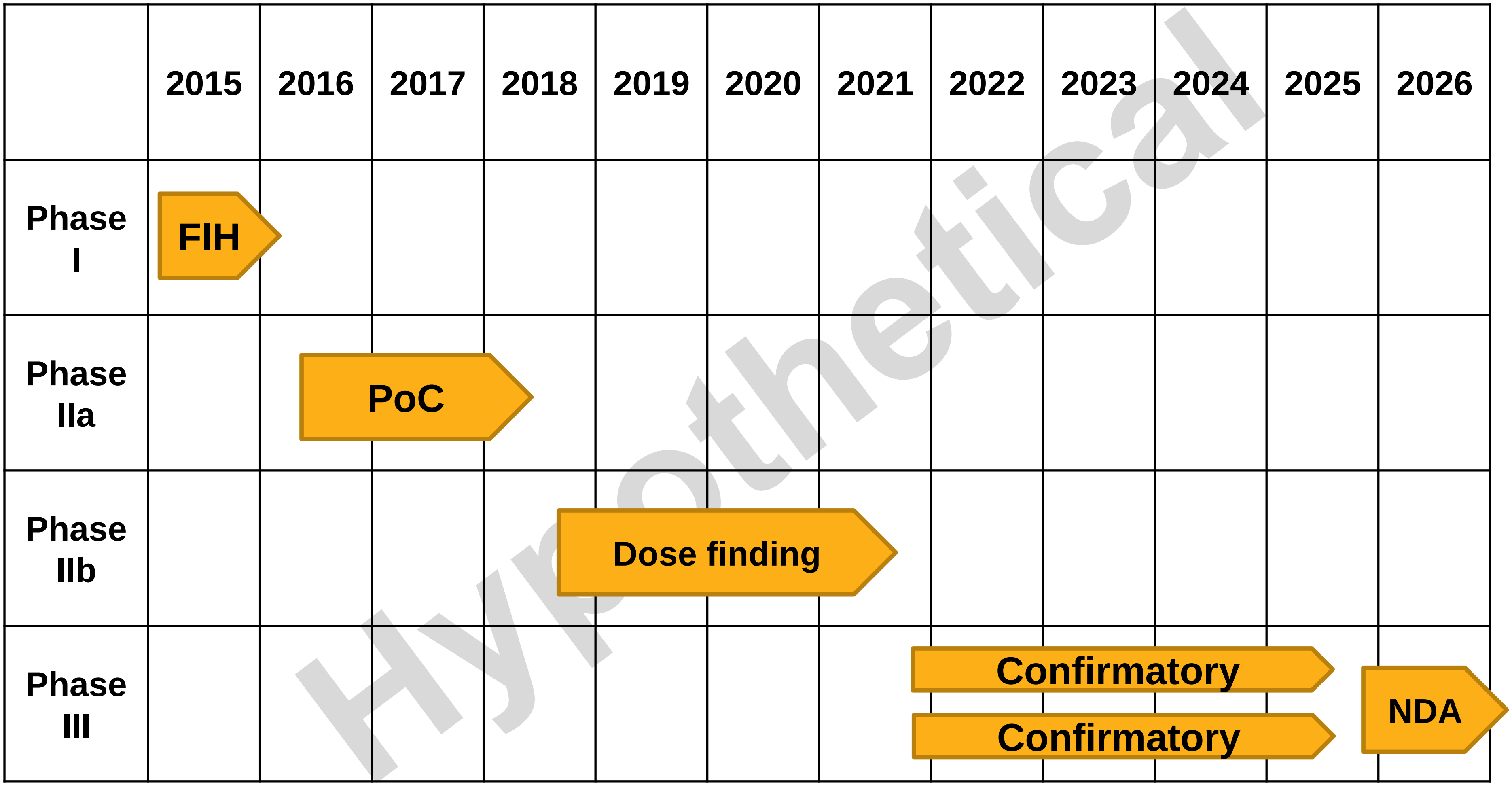
	2015	2016	2017	2018	2019	2020	2021	2022
Phase I	FIH							
Phase IIa		PoC	PoC					
Phase IIb			Dose finding	Dose finding				
Phase III					Confirmatory Confirmatory	Confirmatory Confirmatory	Confirmatory Confirmatory	NDA

Hypothetical

FIH – First in human, PoC – Proof of concept, NDA – new drug application

Traditional Clinical Paradigm for GA

Compound ready now (12 month endpoint): 11+ years



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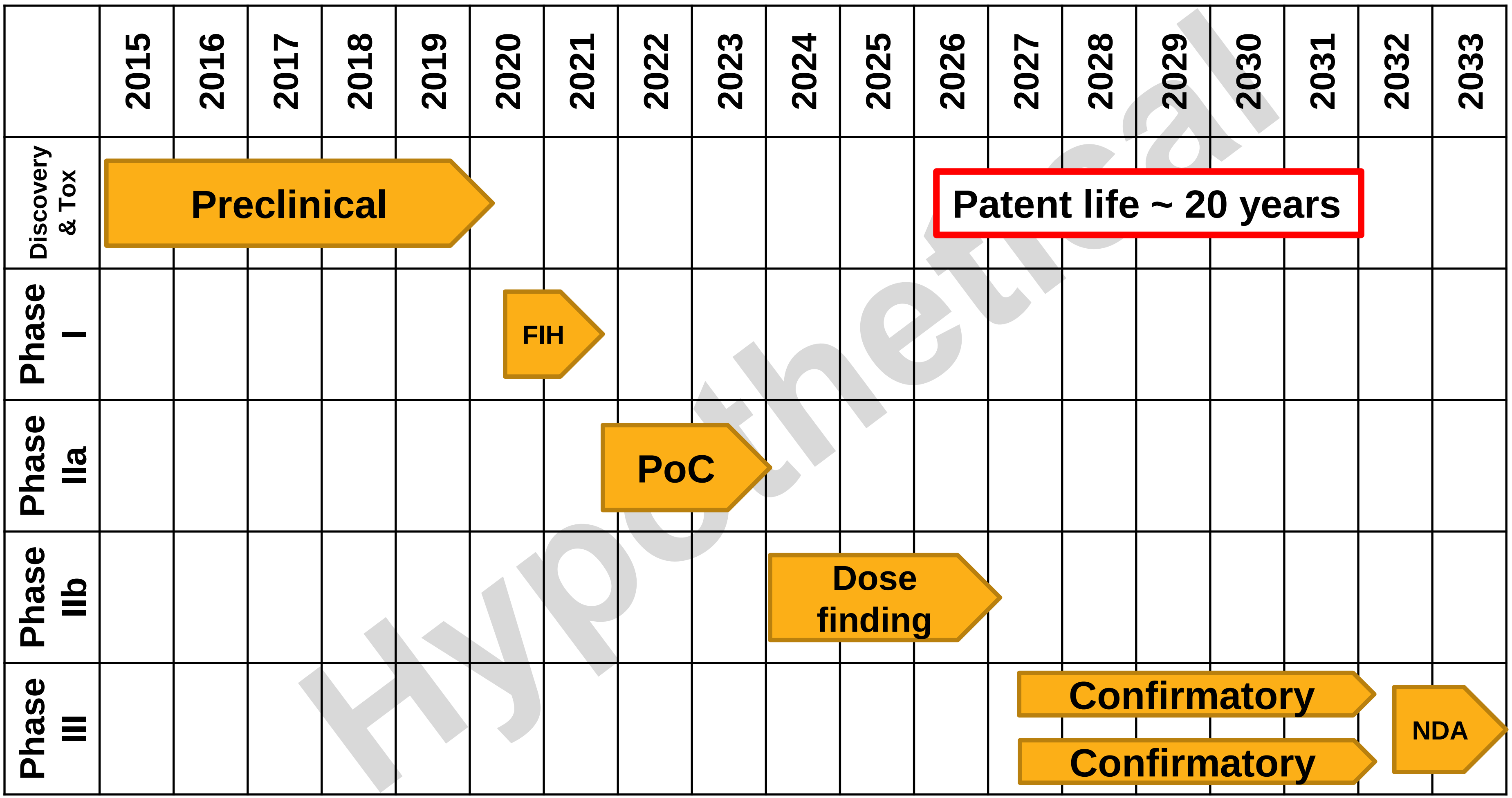
Traditional Clinical Paradigm for GA

Novel target (12 month endpoint): 18++ years

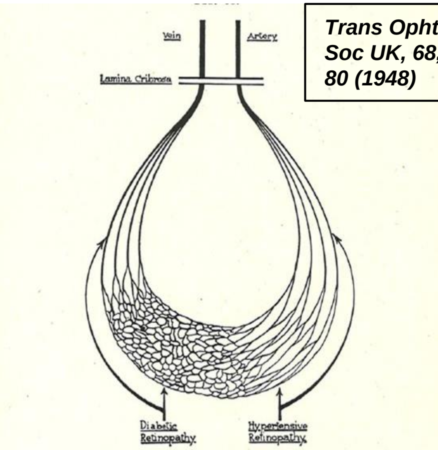


FIH – First in human, PoC – Proof of concept, NDA – new drug application

Target to Therapy Timelines for wet AMD

Example: Ranibizumab

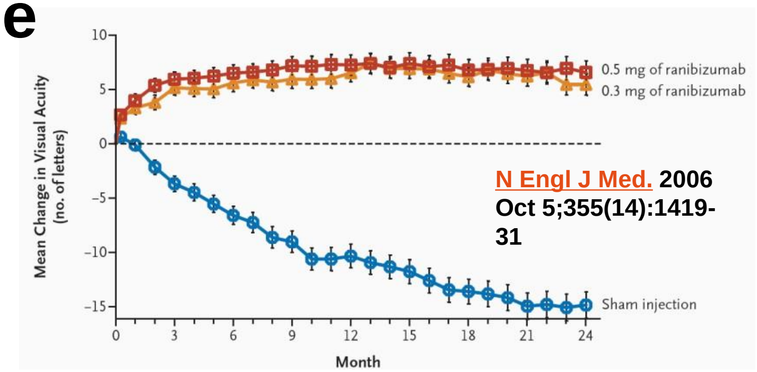
- **1948 - Isaac Michaelson postulates a retinal angiogenic factor**
- **1989 – VEGF identified**
- **1994 – ↑ VEGF associated with neovascular eye disease in patients**
- **1995 – ivt VEGF inhibition prevents retinal neovascularization in mice**
- **2006 – Ranibizumab approved**
- **Target to therapy – 12 - 58 years**



Diagrammatic representation of the retinal vascular system indicating the relationship of arteries and veins to the capillary system and the localization of hypertensive and diabetic affections of the vascular system.

Trans Ophthalmol Soc UK, 68, 137-80 (1948)

(*b*) There is a factor in the retina capable of affecting the growth of new vessels.
(*c*) The factor is associated with the metabolism of the retinal tissue.



N Engl J Med. 2006 Oct 5;355(14):1419-31

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Proof-of- Concept (PoC) studies – where science meets medicine

- **Objective: new medicines quickly to patients**
- **Small-scale clinical trials**
- **Allow a preclinical hypothesis about mechanism of action to be tested**
- **Quickly demonstrate a therapeutic benefit to patients or lack of benefit.**
- **Eliminate compounds with toxicity or other liabilities early in the process.**

Scope of PoC trials

- **Goal: to give confidence to move into larger more expensive clinical trials.**

- **Considerations:**
  - **Duration**

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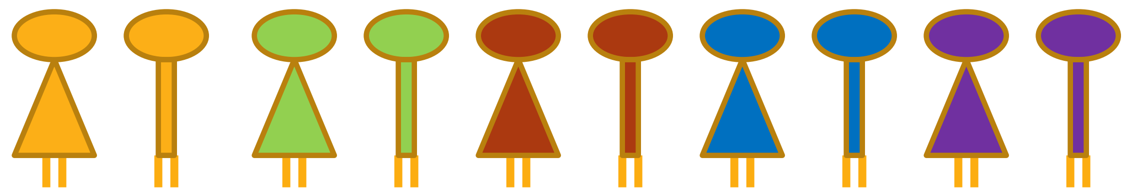
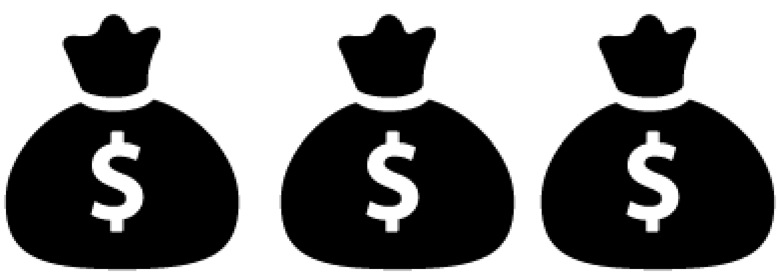
  - **Number of patients**



  - **Cost**



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Requirements for a viable PoC (Phase IIa) trial for GA

- **Visual acuity (BCVA)?**
- **Anatomic measure: fundus autofluoresence (FAF), color photos or OCT?**
- **Functional measures: reading speed, contrast sensitivity, dark adaptation, microperimetry, low luminance visual acuity?**
- **Level of confidence?**
  - **Acceptance of Type I error (false positive, α)**
  - **Acceptance of Type II error (false negative, β)**
- **Subpopulation vs. broad population of dry AMD?**

Sample Size Calculations for GA lesion growth 1 year trial

Power (%)	Difference (%)	α	s.d.	n (1)*
80	20	0.05	1.67	522

- **Assume: mean annual GA growth rate = 1.82 mm^2, s.d. = 1.67**
- **(Dreyhaupt *et al*., Ophthalmic Epidemiology, 12:353–362, 2005)**
- **Calculations performed with: http://hedwig.mgh.harvard.edu/sample_size/js/js_parallel_quant.html**
- **Bonferroni correction for multiple comparisons (* number of comparisons)**

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80	20	0.05	1.0	190

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Sample Size Calculations for GA lesion growth 1 year trial

Power (%)	Difference (%)	α	s.d.	n (1)*	n (2)*	n (3)*	n (4)*
80	20	0.05	1.67	522	664	742	796
80	20	0.05	1.0	190	240	268	294
80	50	0.1	1.0	24	36	42	46
70	50	0.1	1.0	16	24	28	30

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Path from Target to Drug

How do we develop drugs more quickly? Reduce variability.

1. **Endpoints**
   a. **Surrogate endpoints**
   b. **Endpoints with less variability**
   c. **Endpoints with higher sensitivity for detecting change**
   d. **Larger number of patients**

2. **Patient populations**
   a. **Genetically or phenotypically defined subpopulations**
   b. **High risk patients**
   c. **Rapid progressors**

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Path from Target to Drug

How do we develop drugs more quickly?

3. Higher risk PoC (Phase IIa) study design

a. **Less statistical power (fewer patients, higher tolerance of Type I or Type II errors)**

b. **Genetically or phenotypically defined subpopulations**

4. Direct from PoC (Phase IIa) to Confirmatory (Phase III)

a. **Multiple dosing regimens in PoC trial**

b. **Multiple dosing regimens in Phase III trial**

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Requirements for a viable Confirmatory (Phase III) trial for dry AMD

- **Visual acuity (BCVA)?**
- **Anatomic assessments: fundus photos, fundus autofluorescence (FAF), OCT?**
- **Functional measures such as reading speed, contrast sensitivity, dark adaptation, microperimetry, low luminance visual acuity?**
- **Length of trial?**
- **Subpopulation vs. broad population?**

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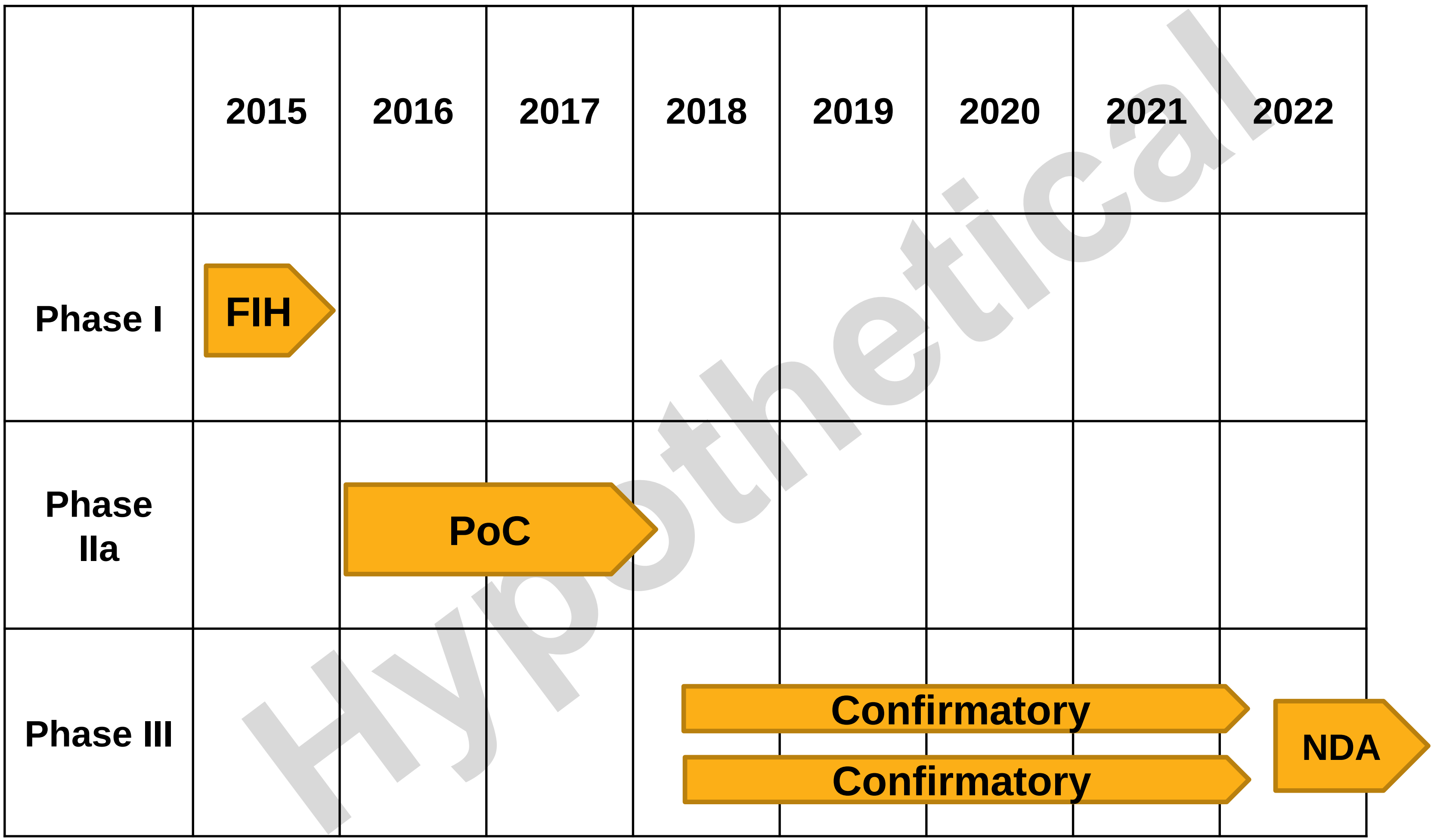
Accelerated Paradigm for GA

Compound ready now (12 month endpoint): ~ 8+ years



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Challenges to overcome

- **Lack of robust animal models**
- **Pathobiology not well understood and likely multifactorial**
- **Single target or multiple targets required for therapeutic effect?**
- **PK (pharmacokinetics) in the eye – are therapeutic levels of drugs reaching the relevant tissue(s)? Complicates dose finding.**
- **No established surrogate endpoints or biomarkers for shorter trials**
- **Genetics: risk factors not causal factors**

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Challenges to overcome

- Visual acuity correlates poorly with dry AMD progression
- Stage at time of intervention (early, intermediate, late AMD)
- Slow progression of disease → long clinical trials
- Variable rate of progression
- Clinical heterogeneity
- Population heterogeneity

→ large number of patients

- Demonstrating patient benefit
- Regulatory and payor expectations

Sample Size Calculations

Power (%)	Difference (%)	α	n (1)*	n (2)*	n (3)*	n (4)*
80	20	0.05	522	664	742	796
80	30	0.05	234	296	332	356
80	40	0.05	132	168	188	202
80	50	0.05	86	108	122	130
80	20	0.1	382	522	608	664
80	30	0.1	170	234	272	296
80	40	0.1	96	132	154	168
80	50	0.1	62	86	100	108

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80	40	0.05	50	62	70	76
80	50	0.05	32	40	46	50
80	20	0.1	138	190	220	240
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80	40	0.1	36	50	56	62
80	50	0.1	24	32	38	40

- **Assume: mean annual GA growth rate = 1.82 mm², s.d. = 1 mm²**
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Sample Size Calculations

Power (%)	Difference (%)	α	n (1)*	n (2)*	n (3)*	n (4)*
70	40	0.05	102	132	150	162
70	50	0.05	66	86	98	106
70	40	0.1	70	102	120	132
70	50	0.1	46	66	78	86

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