

# Quark Clinical Experience with Synthetic siRNAs



- ◆ Overview of Quark development programs
- ◆ Summary of nonclinical and clinical experience in the eye following local (intravitreal) administration
- ◆ Summary of nonclinical and clinical experience following systemic (IV) administration

# Quark Pharmaceuticals

## Candidates in Formal Development



Candidate	Indication	Animal Research	Preclinical	IND	Phase I/IIa	Phase II
PF-655 	Age Related Macular Degeneration	→	→	→	→	→
	Diabetic Macular Edema	→	→	→	→	→
QPI-1002 	Kidney Transplant (DGF)	→	→	→	→	→
	Acute Kidney Injury	→	→	→	→	→
QPI-1007	NAION	→	→	→	→	
	Glaucoma	→	→			
Not disclosed 	Fibrosis	→				

**Robust preclinical pipeline in neuroprotection/regeneration, respiratory diseases, chronic kidney disease and cancer**

# World-wide Clinical Trials of Quark siRNAs



## ◆ UNITED STATES

## ◆ EUROPE

- ITALY
- FRANCE
- SPAIN
- UNITED KINGDOM
- GERMANY
- DENMARK
- SWITZERLAND

## ◆ INDIA

## ◆ ISRAEL

## ◆ SOUTH AMERICA

- PERU
- BRAZIL

***Quark siRNAs have been regulated as NCEs in all countries***

# Patients Dosed with Quark Synthetic siRNAs



- ◆ Via systemic (IV) administration: 149 patients
- ◆ Via intravitreal administration: 350 patients

# Quark Pharmaceuticals

## Candidates in Formal Development



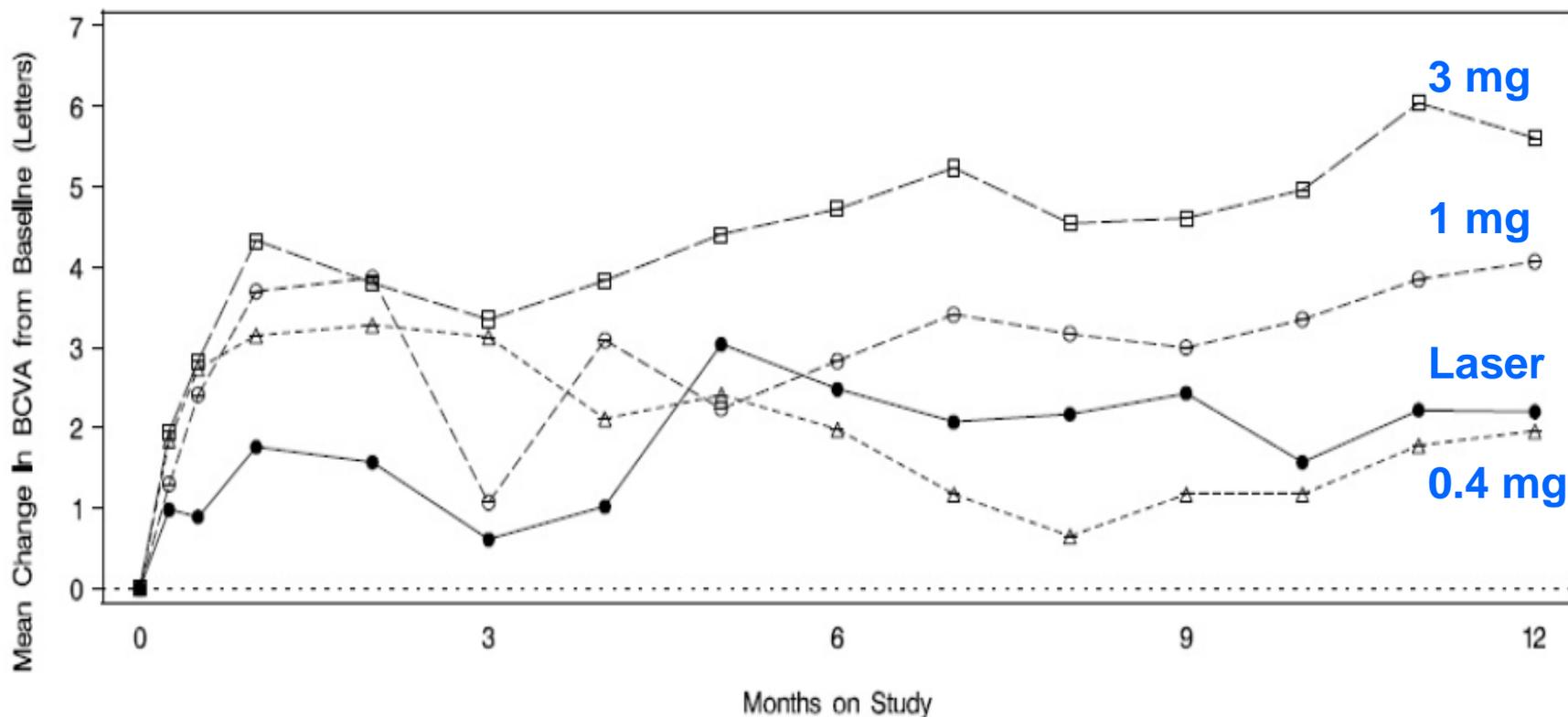
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# Proof of Principle Efficacy in Humans: Durable Improvement in Visual Acuity in Diabetic Macular Edema Patients vs. Standard of Care

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Pharmaceuticals

Mean Change in Visual Acuity from Baseline (LOCF) by Study Visit – Study Eye, ITT Population



Data from DEGAS study following monthly intravitreal dosing



# Comparison of nonclinical and clinical safety data

*Quark*  
Pharmaceuticals



# Quark Pharmaceuticals

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# QPI-1002 Nonclinical Studies

(note: this is a single-administration product)



## ◆ Genotoxicity

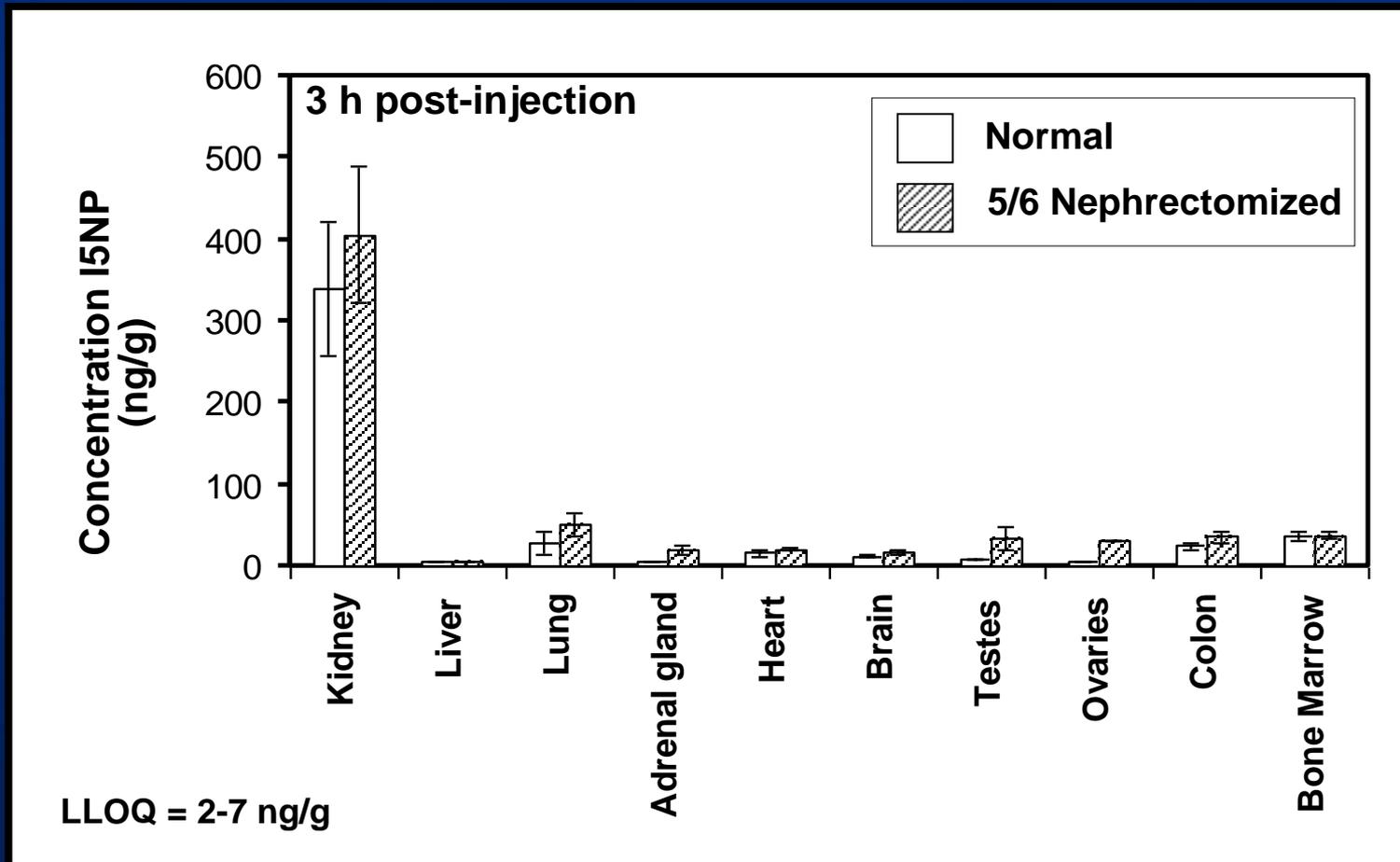
- Ames
- Human lymphocyte chromosomal assay
- Rat micronucleus assay

## ◆ Safety Pharmacology: Monkey Telemetry

## ◆ Toxicology

- Human *in vitro* blood compatibility study
- Rat
  - Subacute (4-dose) IV tox/PK/distribution study in normal rats
  - Subacute (4-dose) IV tox/PK/distribution study in renally-impaired rats
  - Single high-dose IV tox/PK/distribution study
- Monkey
  - Subacute (4-dose) IV tox/PK/distribution study
  - Single high-dose IV tox/PK/distribution study

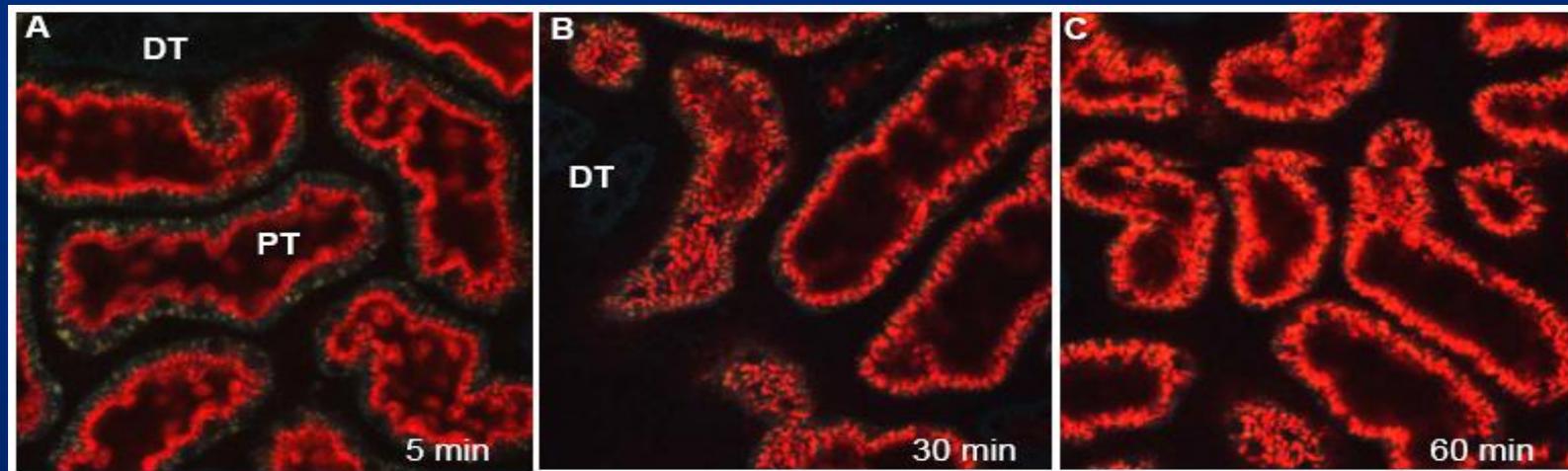
# QPI-1002 Distributes Predominantly to Kidney in Rats After IV Injection



Dose: 10 mg/kg

# siRNA Accumulates in Proximal Tubule Epithelium Following IV Administration

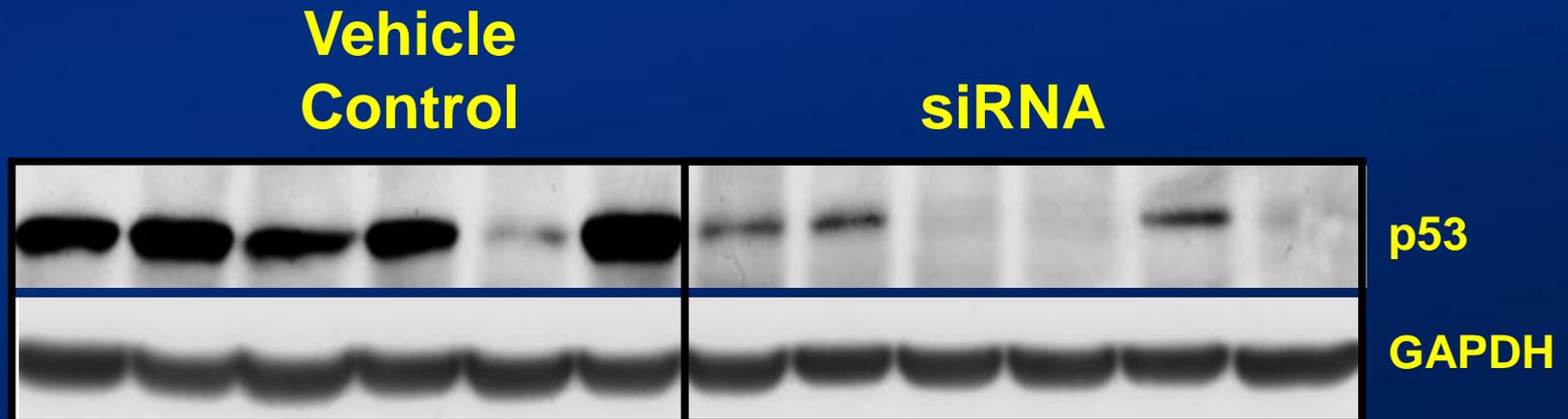
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PT = proximal tubules  
DT = distal tubules

# Inhibition of p53 Protein Expression in Rat Model of Acute Kidney Injury

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- 12 mg/kg siRNA administered 4 hours prior to injury
- Kidneys harvested 24-h post-injury (at time of maximal induction of p53)

# Summary of Acute Toxicity Studies in the Monkey

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Dose (mg/kg)	Human Equivalent Dose (mg/kg)	Findings
3 (x4)	1	No effect
12 (x4)	4	No effect
48 (x4)	16	No effect
200	70	Minimal effects
<b>500</b>	<b>170</b>	<b>NOAEL</b>
1000*	330	<ul style="list-style-type: none"><li>◆ Slight Increase in mean C3a concentration 5 min post-dosing.</li><li>◆ Transient increase in PT and APTT at 5 minutes post-dose.</li></ul>

\*Maximum feasible dose

# Summary of QPI-1002 Clinical Experience



- ◆ Phase I: cardiac surgery: **15** patients dosed
  - Up to 10 mg/kg
  - No dose-limiting toxicities observed
  - Maximum tolerated dose not yet determined
  
- ◆ Phase I: renal transplantation: **40** patients dosed
  - Up to 10 mg/kg
  - No dose-limiting toxicities observed
  - Maximum tolerated dose not yet determined
  
- ◆ Phase II: renal transplantation: **188** patients randomized to-date (actively enrolling)  
10 mg/kg dose level
  - No dose-limiting toxicities observed

***No indication of immune stimulation, interferon induction or complement activation***

# Quark Pharmaceuticals

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# PF-655 Nonclinical Studies



- ◆ Genotoxicity
  - AMEs
  - Human lymphocyte chromosomal aberration
  - Mouse Micronucleus assay
- ◆ Toxicology
  - Rat
    - Acute (single-dose) intravitreal study
    - Acute (single-dose) IV study in rat up to 100 mg/kg
    - A 28-day repeat-dose IV study up to 100 mg/kg
  - Monkey
    - Acute (single-dose) intravitreal study up to 3 mg/eye
    - A 49-Week (13-Dose) intravitreal study with a 13-Week (4-Dose) interim evaluation up to 3 mg/eye

# QPI-1007 Nonclinical Studies



## ◆ Genotox

- Ames
- Human lymphocyte chromosomal assay

## ◆ Toxicology

- Rat
  - A Single-Dose Toxicity Study of QPI-1007 Administered by Intravenous Injection to Sprague-Dawley Rats
  - A 4-Week Study of QPI-1007 Administered by Intravenous Bolus Injection to Rats
- Dutch Belted Rabbit
  - A Single-Dose Toxicity Study of QPI-1007 Administered by Intravitreal Injection to Dutch-Belted Rabbits
  - A 9-month (11-Dose) Intravitreal Injection Toxicity and Toxicokinetic Study of QPI 1007 in Dutch Belted Rabbits

# Summary Toxicology Findings from Quark Ophthalmic Programs



- ◆ No genetic toxicity observed
- ◆ Systemic administration
  - No findings after up to 100 mg/kg bolus IV injection qd x 28
  - Pertains to concerns around potential chronic perturbation of the RNAi pathway*
- ◆ Intravitreal administration
  - Mild mononuclear cell infiltrate in the vitreous and aqueous humor; reversible; not considered adverse
  - Posterior capsular cataract developed in both eyes of one high-dose (3 mg) PF-655 monkey; cause unknown but attributed to test article
  - No Observable Adverse Effect Level (NOAEL)
    - PF-655 in Monkey eye = 1 mg (human equivalent of 2 mg)
    - QPI-1007 in Rabbit eye = 3 mg (human equivalent of 6 mg)

# Summary of Clinical Experience



- ◆ PF-655 (intravitreal injection)
  - Phase I/IIa: 54 subjects dosed
    - Single IVT\* administration
  - Phase II AMD: 120 patients dosed
    - IVT dosing q2w x 5
    - IVT dosing q4w x 3
  - Phase II DME: 138 patients dosed
    - IVT dosing qmonth x 12plus
  
- ◆ QPI-1007 (single intravitreal injection)
  - Phase I: 18 patients dosed
  - Phase IIa NAION: 20 patients dosed to-date (actively enrolling)

**\*IVT = intravitreal injection**

# Summary of Clinical Safety Data from Quark Ophthalmic Programs



## ◆ PF-655

- Up to **3 mg** dose levels evaluated in two Phase 2 repeat-dose studies
- No dose-limiting toxicities (DLTs) observed to date
- Maximum tolerated dose (MTD) not yet determined
- Future directions: enable up to 12 mg dose level to determine:
  - DLTs
  - MTD
  - Dose levels to advance to Phase 3 studies

## ◆ QPI-1007

- Up to **6 mg** dose levels evaluated in Phase I/IIa single-dose studies
- No dose-limiting toxicities observed to date
- Maximum tolerated dose not yet determined
- Future directions: assess clinical activity in target population

# Summary of Quark Clinical Experience with Synthetic siRNAs



- ◆ 593 patients enrolled to-date in Quark/Pfizer/Novartis studies world-wide (499 dosed with siRNAs)
- ◆ No dose-limiting toxicities observed
  - PF-655: 3 mg intravitreal injection
  - QPI-1007: 6 mg intravitreal injection
  - QPI-1002: 10 mg/kg bolus IV injection
- ◆ Maximum tolerated dose not yet determined in:
  - Patients with diabetic macular edema (minimum effective dose = 1 mg/eye)
  - Patients with macular degeneration
  - Cardiac surgery patients
  - Renal transplant patients
  - Patients with non-arteritic anterior ischemic optic neuropathy