How Clinical Trial Methodologies are Changing

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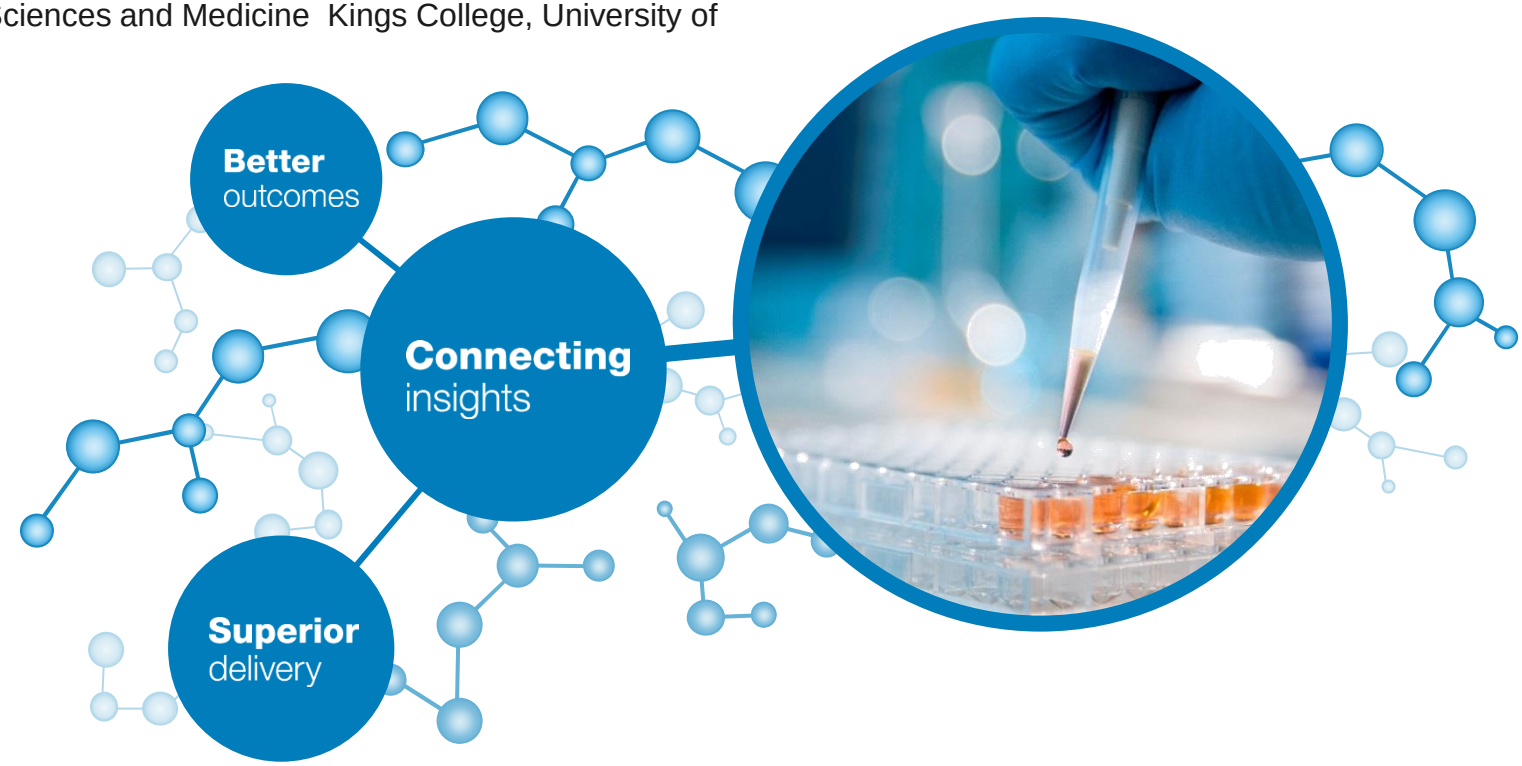

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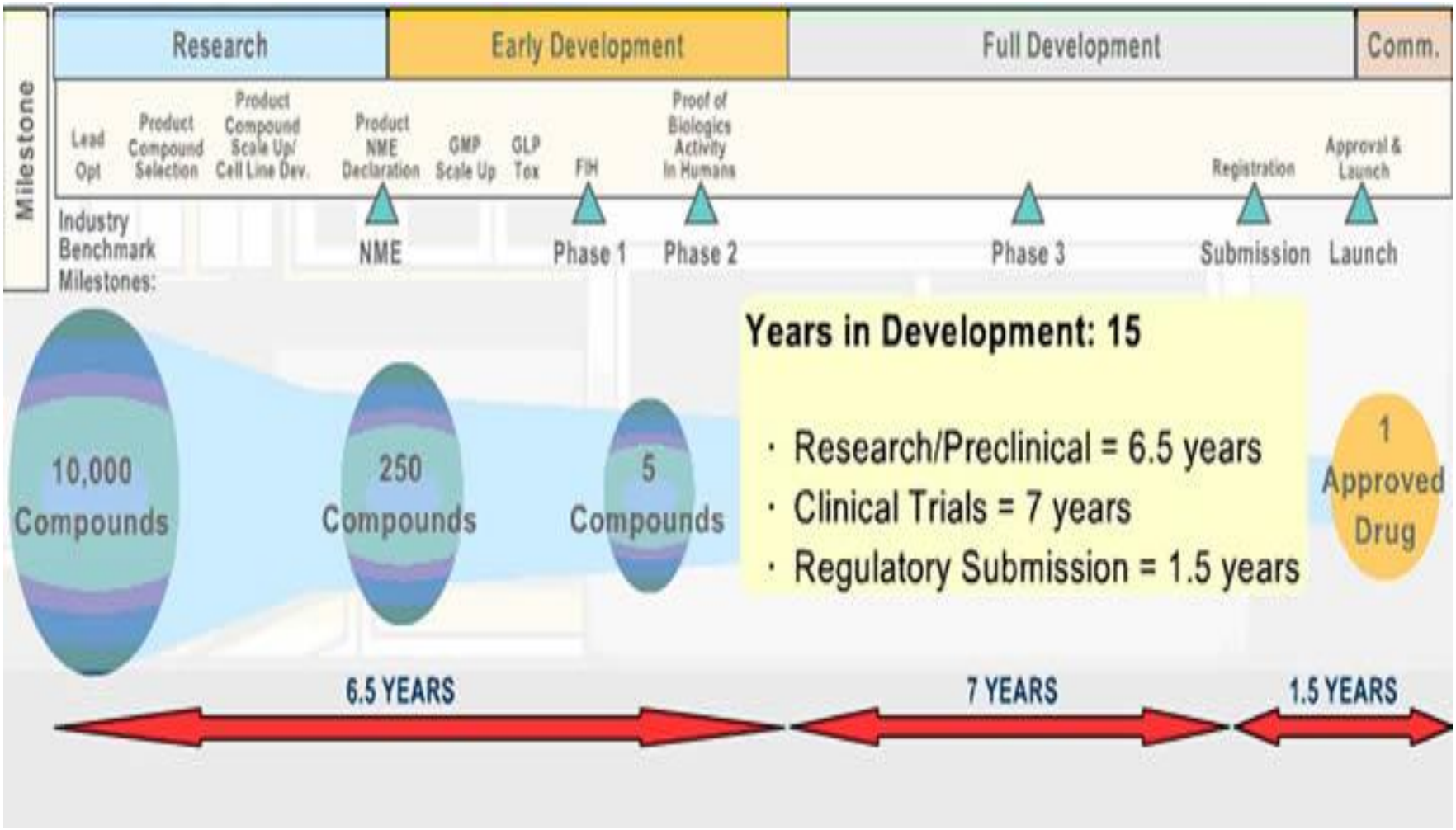
The drug development process



Tufts Center for the Study of Drug Development

Drug discovery remains an expensive undertaking despite ongoing efforts to reduce R&D costs

- Discovery to marketing approval - $ 2.6 billion
  - Average out of pocket expenses $1,400 million
  - Time costs $1,200 million
- R&D process suffers from significant technical risks

Rise in costs driven out of pocket expenses and high failure rate in human testing

- Increased clinical trial complexity
- Larger clinical trials
- Focus on targeting chronic and degenerative diseases
- Changes in protocol design
- Too many late phase failures
- Payer demands on comparative effectiveness data

Source: DiMasi et al., Tufts News November 18, 2014.

Regulatory environment in Europe

Directive 2001/20/EC: The implementation of Good Clinical Practice in the conduct of clinical trials on medicinal products for human use

- Highly regulated increasing complexity and cost and about to change !
- Minimum standard of GCP and GMP for all phases of clinical research
- Investigational products to be manufactured in compliance with GMP
- (cf. USA, Asia-Pacific and BRICS regions)
- Increased regulatory burden (time & costs)
- Variations in application of directive across EU member states adds to confusion and frustration

Clinical Trials Regulations on Medicinal Products for Human Use – 536/2014

- Implementation proposed in 2018
- Purpose: To remove inconsistencies and variations across member states

Clinical development realities

Pipeline pressures have intensified the demand for speed and productivity

+

Companies need better, faster decision-making about which compounds to progress

=

Portfolio productivity requires rigorous, flexible scientific and clinical investigations that deliver optimum quality data and insights to make the correct decisions

>

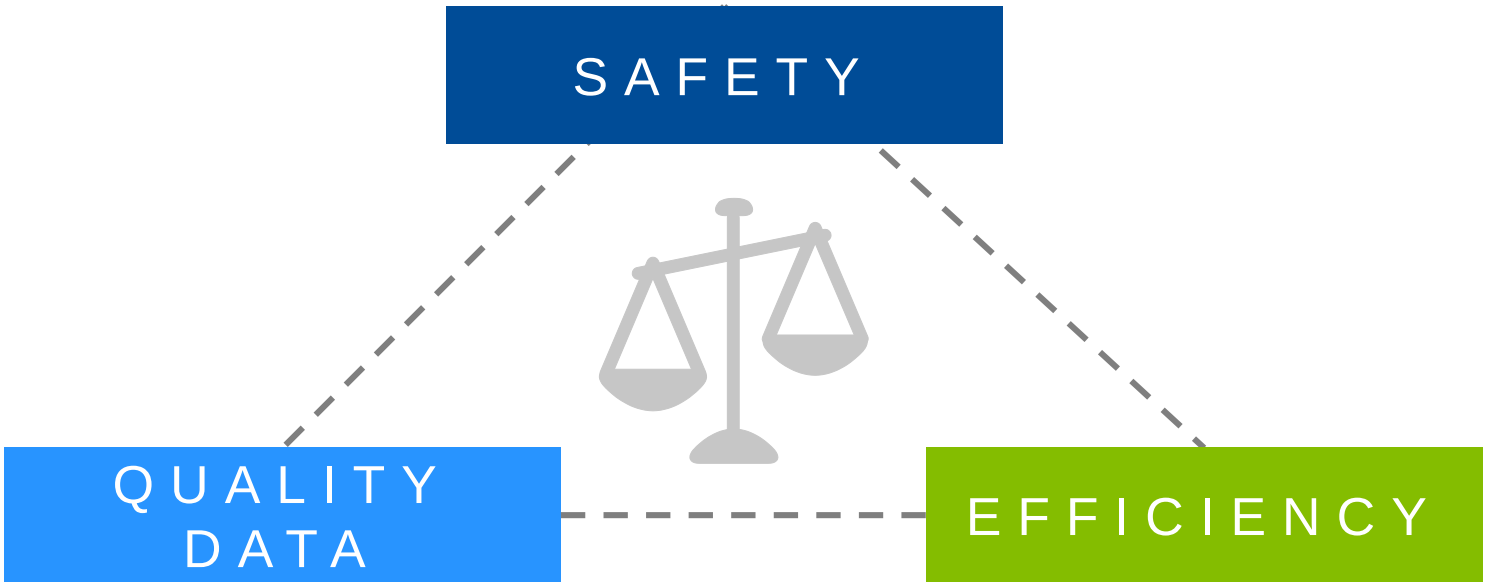
New approaches are needed to:

- Better indicate an investigational drug's viability
- Identify risks and increase compound knowledge
- Facilitate better go/no-go decisions

QUINTILES

Faster, better – safely

Drug development's delicate balancing act



In new drug development, we must all balance getting the data we need as efficiently as possible, without compromising patient safety.

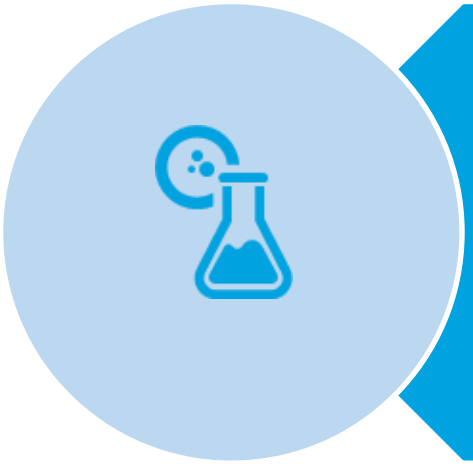
The clinical drug development paradigm is changing

- Advances in science and technologies have led to better understanding of disease and potential successful treatments at the molecular level
  - Personalised medicine

- Development of powerful computer modelling and simulation tools now integrate vast amounts of biological data in a knowledge management system to aid rational drug design and development
  - ***Source: Scientific American Pathways 2010, "Making Medicine More Scientific"***
  - Changing drug development from a linear to an integrated process
  - Merging of traditional clinical development phases

- Innovative clinical trial designs
  - Adaptive flexible protocols
    - Integrated, umbrella, basket protocols
    - Utilizes emerging clinical data to maximize the potential for a successful outcome

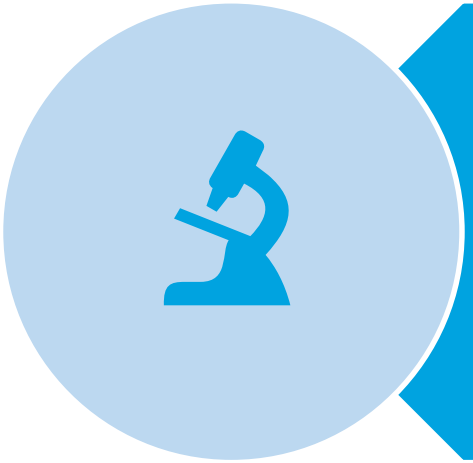
Personalised medicine – it's not new !



The Nairobi Declaration 1984

Drug therapy aims to give:

- the right drug
- to the right patient
- at the right dose
- and at an affordable cost



Personalised Medicine:
"the use of genomic, epigenomic, exposure, and other data to define individual patterns of disease, potentially leading to better individual treatment"

Source: National Academy Sciences (US), 2011

It is the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease, in the biology and/or prognosis of those diseases they may develop, or in their response to a specific treatment. Source: Timmerman 2013

QUINTILES

Personalised medicine

› Why?

- » The clinical response to drug administration varies widely between individuals. The dose that is effective and safe in one patient may be ineffective and unsafe in other patients with the same underlying illness.
- » Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not.
- » Ultimate goal is the tailoring of medical treatment to the individual characteristics of each patient

› How

- » Understand genetic/molecular pathophysiology of the disease
- » Define, confirm and validate target expression in patient population
- » Critique preclinical profile of new molecule for safety and activity
  - – Take into account species selectivity/variation
- » Develop relevant, reproducible response biomarkers of safety, target engagement and efficacy
- » Select appropriate patient population based on the genetic/molecular pathophysiology of the disease

Personalised medicine

- **Aims to reduce the one size fits all approach to drug development and treatment**
- **Will result in changes to the R&D paradigms of the drug development process**
  - From a linear to an integrated process
  - Molecular, pharmacological and clinical data will be integrated in a knowledge management system to aid drug rational drug design
- **Improves efficiency and reduces the cost of drug discovery and development**
  - More success and less failures
  - Reduce development times
- **Improves patient care**
  - Increase in desired outcome
  - Reduced probability of untoward effects

Personalised medicine

- It is possible that in the future diseases will be classified based on their biological mechanism?
- Terms such as liver or pancreatic cancer could become redundant as cancers become better understood at the molecular pathway level, and drug labels could incorporate specific mutations.
  - E.g, recent launch of Vertex's Kalydeco (Jan 2012), is not approved for cystic fibrosis per se, but approved for the 3%-5% of cystic fibrosis patients who have the G551D mutation
- One of the benefits of a more targeted approach to drug development would be a corresponding acceleration of approval times.
- Kalydeco took six years to move from an IND to approval, a process that takes on average 13 years.
  - Highly specific targeting in the form of the G551D mutation, which in turn led to an accelerated approval path which resulted in an FDA approval up three months after submission.

Personalised medicine

- The U.S. Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) approved 41 novel new drugs (NNDs), either new molecular entities or new therapeutic biologics, in 2014.
- Of these 41 NNDs, nine of them --- more than 20 percent --- were personalised medicines as classified by the Personalized Medicine Coalition (PMC).
- One of the consequences of personalised medicine will almost certainly be increased post marketing scrutiny.
  - Smaller phase III studies mean smaller numbers of humans exposed
  - This will require more and better post market data around both effectiveness and safety

The nine newly approved personalised medicines include:

1. **Lynparza (olaparib)** for the treatment of advanced ovarian cancer. The decision to treat with this product is affected by the BRCA biomarker status in patients.
2. **Vimizim (elosulfase alpha)** for the treatment of Mucopolysaccharidosis Type IV (Morquio Syndrome). The decision to treat with this product is affected by the type A or B biomarker status in patients.
3. **Cyrazma (ramucirumab)** for the treatment of advanced gastric or gastro-esophageal junction adenocarcinoma or non-small cell lung cancer (NSCLC). Treatment procedures are influenced by the EGFR or ALK biomarker status in patients.
4. **Zykadia (ceritinib)** for the treatment of NSCLC. The decision to treat with this product is affected by the ALK biomarker status in patients.
5. **Beleodaq (belinostat)** for the treatment of peripheral T-cell lymphoma. Treatment procedures are influenced by the UGT1A1 biomarker status in patients.
6. **Cerdelga (eliglustat)** for the long-term treatment of Gaucher disease type 1. Treatment procedures are influenced by the CYP2D6 biomarker status in patients.
7. **Harvoni (ledipasvir and sofosbuvir)** for the treatment of chronic hepatitis C infection. The decision to treat with this product is affected by the genotype 1 biomarker status of the viral infection in patients.
8. **Viekira Pak (ombitasvir, paritaprevir, and ritonavir; dasabuvir)** for the treatment of chronic hepatitis C infection. The decision to treat with this product is affected by the genotype 1 biomarker status of the viral infection in patients.
9. **Blincyto (blinatumomab)** for the treatment of B-cell precursor acute lymphoblastic leukemia (ALL). The decision to treat with this product is affected by the Philadelphia chromosome biomarker status in patients.

Adaptive Trial Designs

- Classically designed clinical trials may not offer enough **flexibility**
  - › Decisions on sampling measures within a trial are made and **fixed in advance**
  - › In a classical trial patients are allocated equally to one of two different treatments
  - › At the end of the trial , results are analysed and a decision is made as to which treatment is the more effective
  - › **Unable to utilize** emerging knowledge as trial progresses

Adaptive Trial Designs

- **Adaptive trials**
  - A clinical study design that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypothesis based on the analysis of interim data
    - Study eligibility criteria
    - Randomization procedure
    - Treatment regimens
    - Total sample size
    - Schedule of assessments
    - Primary end points
    - Selection of secondary endpoints
    - Methods of analyses
  - Any changes should not be ad hoc, but ‘by design’

Adaptive Trial Designs

- Adaptive designs are not a solution for inadequate planning, but are meant to enhance study efficiency while maintaining validity and integrity

- When considering an adaptive design feasibility, validity, integrity, efficiency and flexibility should be assessed.
  - FDA: Adaptive Design Clinical trials for Drugs and Biologics (Draft guidance 2010)
  - EMA: Reflection paper on methodological issues in confirmatory clinical trials planned with adaptive designs (CHMP/EWP/2459/02- 2007)
- Permits interim analyses of critical data (efficacy, safety)

Adaptive Designs in Clinical Drug Development

- When used appropriately adaptive designs are a useful tool in the overall clinical development program
  - Appealing when credible responses can be observed at an early stage
  - Appealing in early exploratory studies when the outcome is unknown or unsure
  - Ensures the study design is still appropriate for long running trials
  - Allows improvement of patient outcomes without compromising statistical validity in a timely manner
  - Offers significant safety and ethical advantages over standard fixed designs
  - Can lead to improved efficiencies in study delivery and cost
  - Improves the likelihood of success
- Care must be taken when considering adaptive designs:
  - Avoid operational bias
    - Unblinding
    - Type 1 errors
  - May limit identifying gaps in knowledge
  - Does not obviate the need to reflect on the data and the design of a complete development program.

Adaptive Trial Designs

- **Example**
  - › Pre determined scientific outcome is measured which allows **randomisation** to be **directed** towards patients that are enriched with the characteristics **predictive** of a **positive outcome** e.g. tumour type or tumour marker
  - › Ongoing assessment of sample size avoids under or over allocation of patients when statistical power is based on the assessment of a critical variable

- **Fewer** patients exposed towards **less effective** therapy

- **More** data collected on **effective** therapy

- **Reduced** subject numbers

- **Safer**, more **efficient** in terms of time and cost

- More **beneficial** to the **individual** participant and **society**

Case study in Sickle Cell Disease (SCD)

- First in Class NCE
- Study design
  - › Integrated SAD/MAD/POC
  - › Double blind, placebo controlled, randomised, parallel group, ascending single and multiple dose design
- Subjects
  - › 48 Healthy subjects and 8 patients with SCD–SAD-inpatient
  - › 24 Healthy subjects –MAD- up to 14 day dosing- in patient
  - › 24 patients with SCD- MAD- 28 day dosing in and out patient
- Assessments safety, PK and exploratory PD
- Results
  - › Safe and well tolerated
  - › Early evidence of activity
  - › Dosing extending to 90 days in patients

Pharmacokinetics and Pharmacodynamics of GBT440, a Novel Hemoglobin S Polymerization Inhibitor for the Treatment of Sickle Cell Disease, in Healthy Volunteers and SCD Patients

Mira Patel[1], Athiwat Hutchaleelaha[1], Vincent Siu[1], Abel Silva[1], Donna Oksenberg[1], Josh Lehrer-Graiwer[1], Timothy Mant[2], Eleanor Ramos[1]

[1]Global Blood Therapeutics, Inc., South San Francisco, CA 94080, [2]Quintiles Drug Research Unit at Guy's Hospital, London, United Kingdom

Introduction

Sickle cell disease (SCD) is an inherited disorder caused by a point mutation in the β-globin gene leading to the formation of hemoglobin S (HbS). A primary and obligatory event in the molecular pathogenesis of SCD is the polymerization of deoxygenated HbS and the resulting sickling of red blood cells (RBC). Sickle cell disease is characterized by hemolytic anemia and vaso-occlusion leading to progressive end-organ damage with a clinical course of life-long pain, disability, and early death.

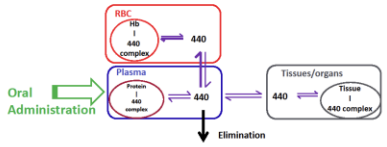
A drug that inhibits HbS polymerization and has pancellular distribution has the potential to provide efficacy. Because oxyhemoglobin is a potent inhibitor of HbS polymerization, allosteric modification of hemoglobin to increase the proportion of oxyhemoglobin is a promising strategy to achieve inhibition of HbS polymerization in all RBCs. By delaying polymerization, the irreversible damage done to the RBC membrane can be prevented and thereby alter the downstream pathophysiology of the disease.

In order to fulfill this unmet need, Global Blood Therapeutics (GBT) is conducting clinical trials for the treatment of SCD with GBT440, an oral small molecule designed to increase the oxygen affinity of Hb, delay Hb polymerization and prevent RBC sickling.

Purpose

- To determine the Pharmacokinetics of GBT440 in Healthy Volunteers and SCD patients
- To evaluate Oxygen Equilibrium Curves as a Pharmacodynamics marker
- To determine PK and PD relationship

Pharmacokinetic Model of GBT440



Methods

SS blood Source

Whole blood (in 3.2 % sodium citrate vacutainers) from sickle cell patients was obtained from the University of North Carolina Comprehensive Sickle Cell Program [Chapel Hill, NC, IRB # BB-0343 (GCRC-101)] or from Sanguine Biosciences, Inc. (Valencia, Ca). The donors were 2-3 months post-transfusion with blood routinely containing 70%-90% HbS and variable amounts of HbA and HbF.

Dose and Patients

Data reported is a subset of data collected in the GBT440-001 clinical trial. Healthy volunteers were dosed with a single dose of 1000 mg of GBT440 and SCD patients were dosed with either a single dose of 1000 mg and with multiple doses of 500, 700 and 1000 mg of GBT440 for 28 days.

Analysis of Blood and Plasma GBT440 Concentrations

Concentration of GBT440 in whole blood and plasma were determined using validated LCMS methods. Concentration of GBT440 in RBCs was calculated using the GBT440 concentrations in blood and plasma.

In vitro Hemoximetry

GBT440 (in 80 mM stocks in 100% DMSO) or DMSO (for controls) was mixed with plasma prior to the addition of autologous RBCs. Samples were then incubated in a 37 °C water bath and gently shaken for one hour. After incubation, the samples were diluted in a 30 mM TES buffer. Diluted samples were loaded into Hemox Analyzer (TCS Scientific, New Hope, PA) cuvettes and oxygenated for 20 minutes using compressed air. After oxygenation, the samples were deoxygenated using nitrogen gas until the pO_2 reached 1.6 millimeters of mercury (mm Hg). During the deoxygenation step, data was collected into Oxygen Equilibrium Curve (OEC) files using the Hemox Analytical Software (HAS). OEC files from the various data sets were analyzed to determine the p20, and p50 values. Delta values were obtained by subtracting the control p20 or p50 from the sample p20 or p50 value.

Clinical Hemoximetry

Blood samples collected in sodium citrate vacutainers were kept at 4°C until analysis. Clinical trial samples were analyzed within 12-43 hours of the draw. Following hematocrit (Hct) determination, the samples were then diluted 50 or 100-fold based upon the Hct into 37°C TES buffer (30 mM TES, 130 mM NaCl, 5 mM KCl, pH 7.4). Samples were subsequently transferred to the Hemox Analyzer sample chamber where they were saturated with compressed air for 20 minutes and then deoxygenated with pure nitrogen. During the deoxygenation step, data was collected into Oxygen Equilibrium Curve (OEC) files using the Hemox Analytical Software (HAS). OEC files from the various data sets were analyzed to determine the p20, and p50 values. Delta values for % Hb modification calculations were obtained by subtracting the Day -1 p20 or p50 from the sample p20 or p50 value .

Data Analysis of Clinical Samples

OEC files from the clinical samples were analyzed to determine the p20, and p50. $[GBT440]_{RBC}$ was calculated using $[GBT440]_{tumor}$ $[GBT440]_{plasma}$ and Hct.

Results and Discussion

PHARMACOKINETICS STUDIES

Pharmacokinetics of GBT440 in Healthy Volunteers and SCD Patients after Single and Multiple Doses

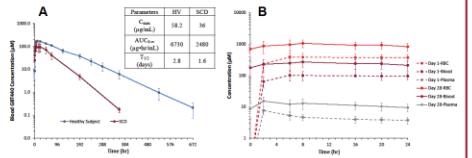


Figure 3:
(A) Mean ± SD Blood Concentration time Profiles of GBT440 in Healthy Volunteers and SCD Patients Following an Oral Administration of 1000 mg. Inset Table shows the PK parameters derived from these profiles. The difference in PK between Healthy Volunteers and SCD Patients is likely due to lower hematocrit and more rapid turnover of RBC in SCD patients. **The long half-life in Healthy Volunteers and SCD Patients supports once daily dosing.** (B) Mean ± SD GBT440 Concentrations on Day 1 and Day 28 following daily dosing of 700 mg in SCD patient. Exposure of GBT440 was ~3-fold higher at steady-state compared to Day 1. The RBC/Plasma ratio was 75:1

		Healthy Volunteers			SCD Patients
Dose (N)		300 mg (6)	600 mg (5)[a]	900 mg (5)[a]	700 mg (11)[b]
C_{max} µg/mL	Mean	97.9	209	294	84.6
	%CV	14.4%	13.5%	9.4%	40.4%
AUC_{0-24} hr*µg/mL	Mean	2149	4359	5968	1771
	%CV	12.3%	11.1%	7.4%	42.5%

Table 1:
PK parameters in whole blood at steady state (Day 15 or Day 28) for healthy volunteers and SCD patients. A dose dependent increase in C_{max} and AUC is observed. Compared to healthy volunteers , patients have a higher %CV. **This high %CV is likely due to differences in RBC turnover and hemolytic rates.**

[a]Excluded subjects who discontinued study drug due to an adverse event
[b]Excluded subject due to dose reduction

IN VITRO PHARMACODYNAMIC MODEL

Oxygen Equilibrium Curves of GBT440 in SS Blood and the Correlation to % Hb modification

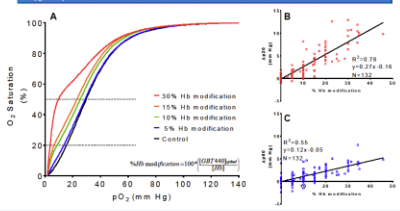


Figure 2:
(A) OECs show the dose-dependent increase in oxygen affinity as evidenced by decreasing p50 and p20 values. Due to the nature of biphasic curves, **p20 is a more sensitive parameter than p50 at lower GBT440 concentrations.** (B and C) Change in p20 (B) and change in p50 (C) at various % Hb modifications. The different correlations (R^2 of 0.78 for Δp20 and R^2 of 0.55 for Δp50) indicate that in the efficacious range Δp20 will be a better predictor of % Hb modification. The equation, y=-0.27x-0.16, was used to calculate % Hb modification in the clinical trial.

IN VIVO PHARMACODYNAMIC DATA

Pharmacodynamics at Steady State in SCD Patients

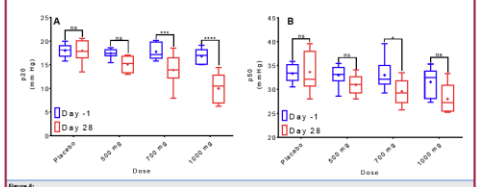


Figure 4:
A summary of the p20 and p50 values observed in SCD subjects after 28 days of dosing. **A dose-dependent decrease in p20 and p50 is observed, showing that increasing levels of drug leads to increased oxygen affinities.** Sidak's multiple comparisons tests were used to measure statistical significance

IN VIVO PHARMACOKINETIC/PHARMACODYNAMIC MODEL

Pharmacokinetics Correlates with Changes in Hb-O_2 Affinity

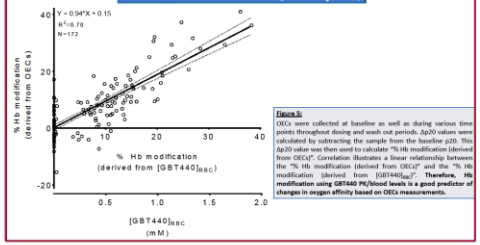


Figure 5:
OECs were collected at baseline as well as during various time points throughout dosing and wash out periods. Δp20 values were calculated by subtracting the sample from the baseline p20. This Δp20 value was then used to calculate "% Hb modification (derived from OECs)". Correlation illustrates a linear relationship between the "% Hb modification (derived from OECs)" and the "% Hb modification (derived from $[GBT440]_{RBC}$)". **Therefore, Hb modification using GBT440 PK/blood levels is a good predictor of changes in oxygen affinity based on OECs measurements.**

Conclusions

- **GBT440 demonstrates linear, dose-proportional PK in Healthy Volunteers and SCD patients (see poster #P371)**
- **GBT440 has a half-life of 2.8 and 1.6 days in Healthy Volunteers and SCD Patients, respectively, which supports once daily dosing**
- **The relatively high %CV in SCD patients (~40%) compared to Healthy Volunteers is likely due to differences in RBC turnover and hemolytic rates**
- **At the predicted therapeutic range (10-30% Hb modification), p20 is a more sensitive indicator of the GBT440-induced left shift in the Hb OEC than p50**
- **A dose-dependent decrease in p20 and p50 is observed, indicating that increasing GBT440 blood levels lead to increased oxygen affinities**
- **% Hb modification using GBT440 PK/blood levels is a good predictor of changes in oxygen affinity based on OECs measurements**

To access the poster digitally, please use the following QR code

A Subcutaneously Administered Investigational RNAi Therapeutic (Fitusiran, ALN-AT3) Targeting Antithrombin for Treatment of Hemophilia: Interim Weekly and Monthly Dosing Results in Patients with Hemophilia A or B

K John Pasi[1], Pencho Georgiev[2], Tim Mant[3], Michael Desmond Creagh[4], Toshko Lissitchkov[5], David Bevan[6], Steve Austin[7], Charles R Hay[8], Brigit Brand[9], Rashid Kazmi[10], Pratima Chowdary[11], Margaret Ragni[12], Jihong Chen[13], Akin Akinc[13], Benny Sorensen[13] and Savita Rangarajan[14]

[1]Royal London Haemophilia Centre, London, United Kingdom; [2]University Multiprofile Hospital for Active Treatment “Sveti Georgi’, Plovdiv, Bulgaria; [3]Quintiles Drug Research Unit, London, United Kingdom; [4]Royal Cornwall Hospitals NHS Trust, Truro, United Kingdom; [5]Clinical Hematology Clinic Specialized Hospital for Active Treatment of "Joan Pavel", Sofia, Bulgaria; [6]Guy's and St Thomas' Hospital NHS Trust, London, United Kingdom; [7]St. George’s Healthcare NHS Trust Haemophilia Centre, London, United Kingdom; [8]Manchester Royal Infirmary, Manchester, United Kingdom; [9]University Hospital, Zurich, Switzerland; [10]University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom; [11]Royal Free Hospital, London, United Kingdom; [12]University of Pittsburgh and Hemophilia Center of Western Pennsylvania, Pittsburgh, PA; [13]Alnylam Pharmaceuticals, Cambridge, MA; [14]Hampshire Hospitals NHF Foundation Trust, Basingstoke, United Kingdom

December 7, 2015 | ASH 2015 | Orlando, FL

Alnylam® PHARMACEUTICALS

Fitusiran

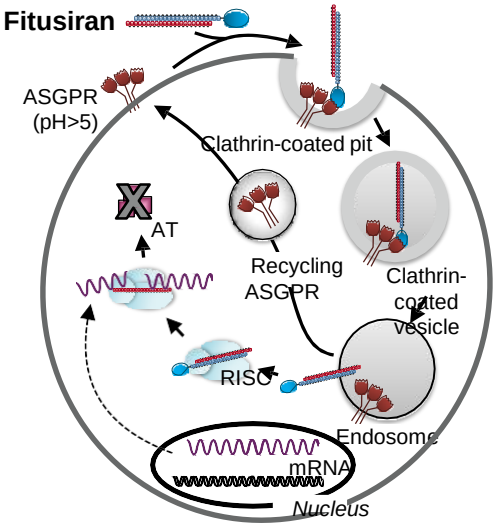
Investigational RNAi Therapeutic for the Treatment of Hemophilia

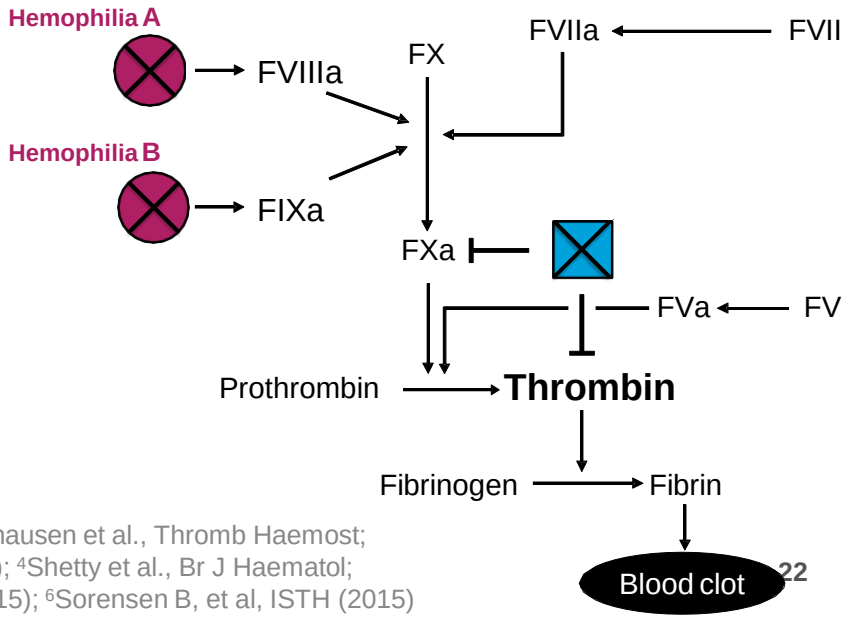
Fitusiran (ALN-AT3)

- SC-administered small interfering RNA (siRNA) therapeutic targeting antithrombin (AT)
  - Non-biologic, chemically-synthesized, with targeting ligand to specifically deliver to liver—the site of AT synthesis
  - Harnesses natural RNA interference (RNAi) mechanism for regulation of plasma AT levels

Therapeutic hypothesis

- Hemophilia A and B are bleeding disorders characterized by ineffective clot formation due to insufficient thrombin generation
- Fitusiran is designed to lower AT, with the goal of promoting sufficient thrombin generation to restore hemostasis and prevent bleeding
  - Observation of ameliorated bleeding phenotype in patients with co-inheritance of thrombophilic traits in hemophilia[1-4]
  - Supported by pre-clinical data[5] and emerging Phase 1 clinical results[6]





[1]Kurnik et al., Haematologica; 92:982-5 (2007); [2]Ettingshausen et al., Thromb Haemost; 85:218-20 (2001); [3]Negrier et al., Blood; 81:690-5 (1993); [4]Shetty et al., Br J Haematol; 138:541-4 (2007); [5]Seghal et al., Nat Med, 21:492-7 (2015); [6]Sorensen B, et al, ISTH (2015)

Fitusiran Phase 1 Study

- Dose-Escalation Study in Four Parts

Part A: Single-Ascending Dose (SAD) | **Randomized 3:1, Single-blind, Placebo-controlled, Healthy volunteers**

30 mcg/kg x 1 SC, N=4 ✓

Part B: Multiple-Ascending Dose (MAD) – Weekly dosing | **Open-label, Patients with Hemophilia A or B**

15 mcg/kg qW x 3 SC, N=3 ✓

45 mcg/kg qW x 3 SC, N=6 ✓

75 mcg/kg qW x 3 SC, N=3 ✓

Part C: MAD – Monthly dosing | **Open-label, Patients with Hemophilia A or B†**

225 mcg/kg qM x 3 SC, N=3 ✓

450 mcg/kg qM x 3 SC, N=3 ✓

900 mcg/kg qM x 3 SC, N=3 ✓

1800 mcg/kg qM x 3 SC, N=3 ✓

80 mg qM x 3 SC, N=6 ✓

Part D: MAD – Monthly dosing | **Open-label, Patients with Hemophilia A or B with inhibitors**

50 mg qM x 3 SC, N=6

80 mg qM x 3 SC, N=6

Ongoing

QUINTILES

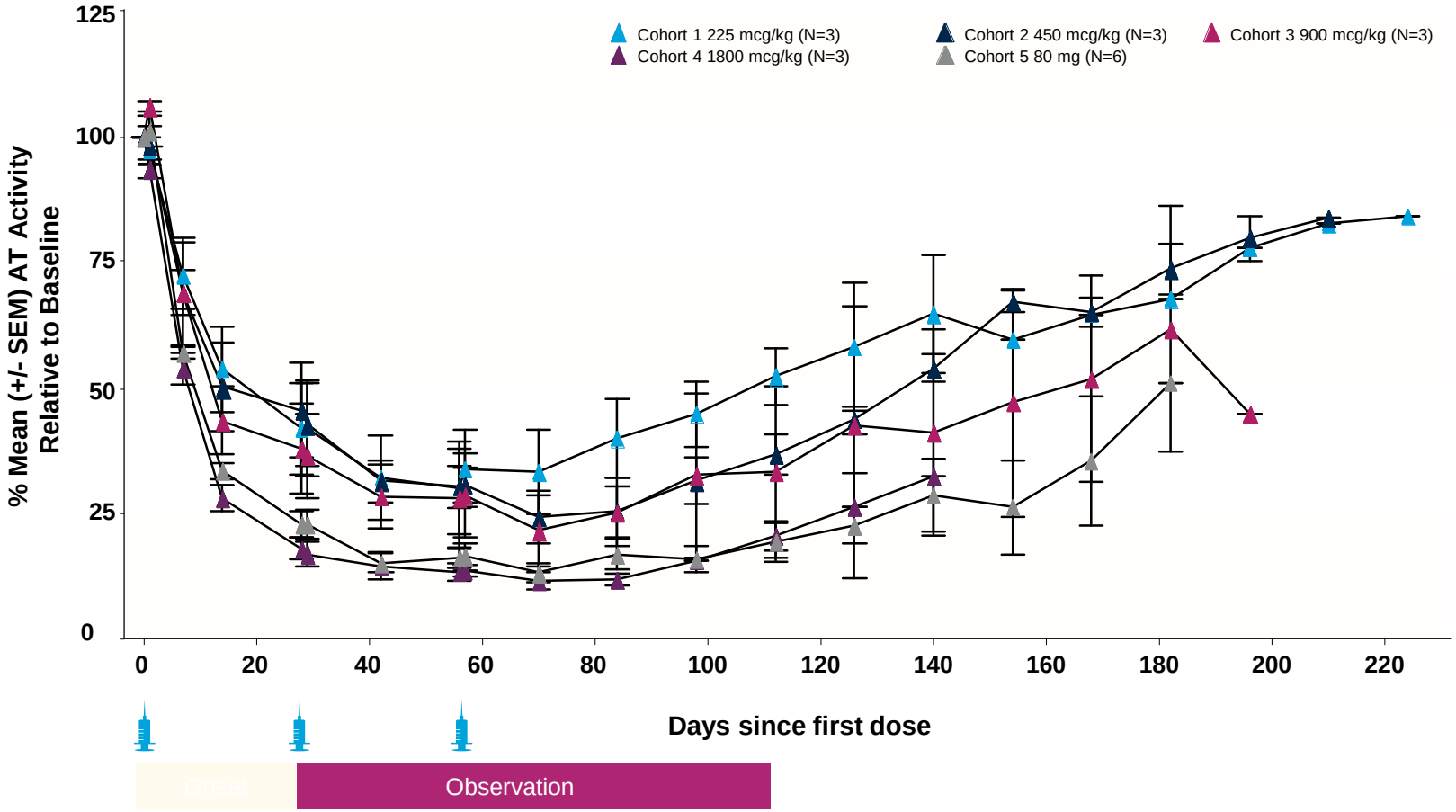
† 5 patients participating in Part C previously participated in Part B

qW, weekly; qM, monthly; SC, subcutaneous

Interim Fitusiran Phase 1 Study Results*

- AT Lowering, Part C

AT lowering after monthly dosing in patients with hemophilia A and B



QUINTILES

*Data transfer: 30Jun2016

Fitusiran Phase 1 Study*

- Summary of Interim Results

Fitusiran generally well tolerated in hemophilia A and B patients with and without inhibitors

- No SAEs related to study drug; no thromboembolic events
- AEs (excluding ISRs) in ≥10% of patients: upper respiratory tract infection (10%) and arthralgia (10%); majority mild or moderate in severity
- 11 (35%) patients reported mild drug-related ISRs
  - Mostly pain and/or erythema at the injection site
- 1 discontinuation due to AE; event resolved in this patient with symptomatic management

Evidence of clinical activity and potential correction of hemophilia phenotype in non-inhibitor patients

- Dose-dependent AT lowering and thrombin generation increase achieved, with once-monthly subcutaneous dose regimen; fixed 80 mg dose provides consistent AT lowering >75%
- In exploratory post-hoc analysis in monthly dose cohorts, fitusiran achieved median ABR = 0, with 53% patients bleed-free and 82% patients experiencing zero spontaneous bleeds

Encouraging early data in inhibitor patients

- AT lowering and thrombin generation increase consistent with non-inhibitor patients
  - Thrombin generation increases consistently exceed those achieved transiently with BPA administration
- Exploratory post-hoc analysis shows 49-100% reduction of bleeds at initial 50 mg dose
- Second cohort (N=6) now fully enrolled at 80 mg

QUINTILES

*Data transfer: up to 11Jul2016

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