PhUSE

Single Day Event – Chennai

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The TGV train of Drug Development

TGV: Train á Grande Vitesse

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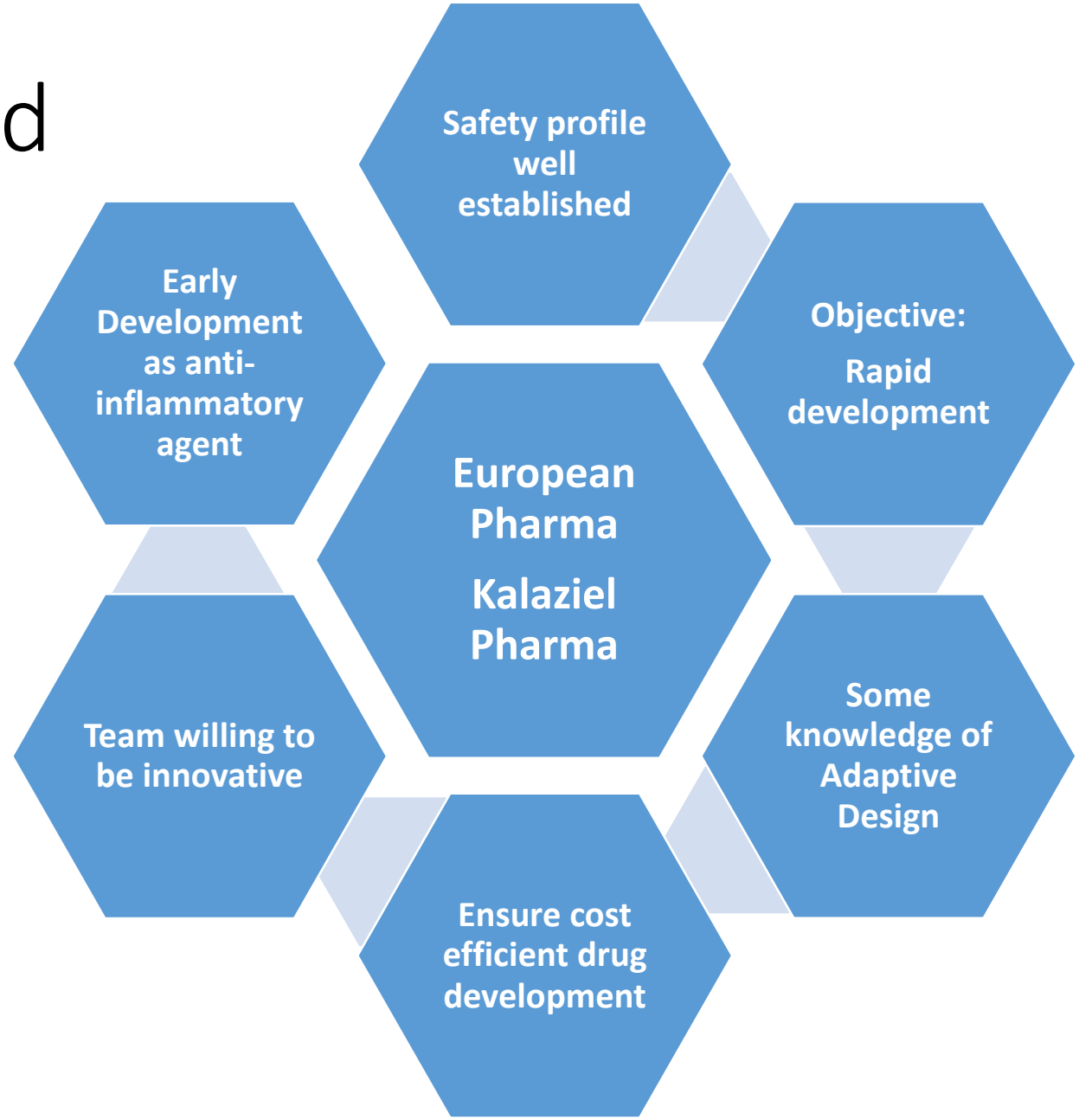
Background



Kalaziel: Angel with the power to thwart demons of disease

Context

History

- brinda was developed in the early ‘80s as an anti-inflammatory agent testing its potential in rheumatic diseases, though three trials did not show any significant effect of brinda in the primary efficacy endpoints

Possibilities

- In the late 90’s the literature indicated a possible role of MCP-1/CCL2 in several inflammatory conditions, and the discovery that brinda anti-inflammatory effects in vitro and in vivo were related to the inhibition of MCP-1/CCL2 production – the clinical development was re-initiated

Innovative design suggested

Seamless Phase II and III

- Time Saved
  - Reporting Phase 2
  - Presenting to management
  - regulatory agencies
  - preparing new protocols for Phase III
  - Finding new sites
  - Submit to IRB’s
  - Submit to Ethics Committees
  - Ramp up / enroll new patients

Innovative design suggested

Seamless Phase II and III

- Greater efficiency in trial design
  - More patients funneled to effective doses earlier?
  - Robust safety database with fewer patients overall?
  - Considering eliminating noise factors – could otherwise be introduced through a new select patient population
  - “re-use” the patient populations
  - Logistical issues as for re-randomization
  - Hangover effects

Definition: seamless phase II/III design

Adaptive seamless Phase II/III design.

- Learning and confirmatory phase in a single trial
- Improve selection of target doses and selections of patients in phase III.
- Modification to treatment schedule, result in greater chance of safe and efficacious treatment.
- II/III analyzed together
- Inferentially seamless

Definition: seamless phase II/III design

Operationally seamless Phase II/III design.

- Continuous in enrollment – direct transition from phase II to phase III
- I.e. operationally seamless
- Analyzed separately and independently

Design issues

Feasibility

- Fast enrollment / long follow up
- Short term endpoints or time to event endpoints

Modifications

- Changes in inclusion/exclusion criteria – retaining trial interpretability
- Modification in adaptively designed trail

Implementation

- Analysis / possible modifications – DSMB or Sponsor
- Regulatory interactions during trial conduct
- Blinding of patients, investigators and sponsor staff

Analytical issues

Alpha level

- Control of type I error rates

Specified rules versus guidelines

- Rules: control of type I error rates
- Some unexpected modifications are permitted, though type I error rates still need to be controlled
- Traditional phase II and III paradigm doesn’t require any pre-specified rules

Combining information

- Combination tests control type I error but contradict scientific rationale
- Sufficient test statistics requires to be followed

Monitoring issues

Roles of DSMB

- Patient safety, scientific rigor.
- Elimination of ineffective study arms to ensure adequate information for optimal benefit-to-risk evaluations (using drop the “looser”)

Considerations

- Probability of success
- Developments costs and time-to-market
- Financial planning, e.g. additional funding, sites etc. due to sample size increase

Communications

- DSMB and Sponsor
- Sponsors and investigators

Brinda - focus on treating diabetic nephropathy

Seamless phase II/III design suggested

Substantial safety data present (indication as an inflammatory agent)

EMA advisory meeting - March 2010

- Some adjustment to the statistical analysis was suggested
- General concept – adaptive seamless Phase II/III was accepted

Brinda - focus on treating diabetic nephropathy

Pivotal trial 1 – phase II/III seamless, adaptive design, randomized, double blind, placebo-controlled parallel group design over a 56 week period.

Pivotal trial 2 – phase III, randomized, double-blind, parallel group study over a 24 week period, starting when most preferable dose of brinda have been selected of interim analysis from pivotal trial 1 (24 week analysis)

Conclusion

- The suggested development plan was accepted
- Enabling Kalaziel Pharma to move seamlessly from phase II to phase III
  - Cutting the time to market by at least 8 months
  - Considerable cost savings
    - No need for new sites
    - No need for recruiting patients for Pivotal trial 1 for phase III
    - For Pivotal trial 1, cost reduction of at least 35%