OUTLOOK

A decade of innovation in pharmaceutical R&D: the Chorus model

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Abstract | Chorus is a small, operationally independent clinical development organization within Eli Lilly and Company that specializes in drug development from candidate selection to clinical proof of concept. The mission of Chorus is to achieve proof of concept rapidly and at a low cost while positioning successful projects for 'pharma-quality' late-stage development. Chorus uses a small internal staff of experienced drug developers and a network of external vendors to design and implement chemistry, manufacturing and control processes, preclinical toxicology and biology, and Phase I/II clinical trials. In the decade since it was established, Chorus has demonstrated substantial productivity improvements in both time and cost compared to traditional pharmaceutical research and development. Here, we describe its development philosophy, organizational structure, operational model and results to date.

Without a dramatic increase in research and development (R&D) productivity, the pharmaceutical industry cannot sustain sufficient innovation to replace the loss of revenues due to patent expirations for successful products[1–5]. The key to tackling this problem is to substantially increase the number and quality of innovative, cost-effective new medicines in development while controlling R&D costs.

Unfortunately, industry performance points to an ongoing and worrisome trend in the opposite direction. As outlined by Paul *et al.*[2], a substantial increase in productivity (P) is necessary for the pharmaceutical industry to achieve (or afford) the numbers of compounds required to achieve sustainable new molecular entity (NME) launch goals. Maintaining sufficient work in process (WIP) while simultaneously reducing cycle time (CT) and cost (C) is necessary. Thus, the key to improving productivity is to have sufficient WIP in the early phases of clinical development, and to efficiently (that is, at low cost) select molecules that will have a higher probability of technical success — p(TS) — in late-stage development (equation 1).

$$P \propto \frac{WIP \cdot p(TS) \cdot V}{CT \cdot C} \quad (1)$$

Chorus is a small, operationally independent integrated drug development organization within Eli Lilly and Company (Lilly) that specializes in drug development from candidate selection to clinical proof of concept (POC). The Chorus model was designed specifically to markedly improve the efficiency of risk discharge (absolute Δp(TS)/CT × C) before the key Phase II decision point. In simple terms, Chorus seeks to drive the largest positive or negative change in p(TS) in the shortest time and at the lowest cost — termed 'lean-to-proof-of-concept' (L2POC).

Building a productivity-focused model involved approaching development, decision-making and implementation in a different fashion. Integrated development plans were needed that sequenced work differently, limited parallel processing, discharged technical risk earlier, and gated spending. The new model required a focus on delivering the minimum data package to discharge key risks and constructing development plans that focused on delivering this at the lowest spend in the shortest time. We believe Chorus was the first to dub this development approach 'truth seeking', in contrast to the 'success-seeking' industry norm where development is planned and proceeds with the assumption of achieving success[6–10]. The efficient implementation of this new approach required the creation of a smaller, more nimble, lower-cost and highly networked model. Such an approach, when operated at scale, is the underpinning of the productivity 'solution', the R&D 'sweet spot' suggested by Paul *et al.*[2] (FIG. 1).

Chorus began in 2002 as an initiative within Lilly's e.Lilly division, which focused on the exploration of alternative R&D approaches in the pharmaceutical industry. Lilly recognized that certain development projects (for example, novel targets with uncertain clinical indications, projects with a history of marginal results, projects outside core areas of interest, etc.) presented challenges owing to the competing R&D investment priorities of a robust internal candidate pipeline.

Chorus began with a small group of individuals and focused on deprioritized assets, and at the outset it operated 'below the radar'. This small-scale, low profile with an initial focus on languishing assets gave Chorus the freedom to develop a radically different approach to translational and early-phase clinical development. The founding principles of Chorus have remained remarkably constant over time:

- focus on development plans to address the points of greatest influence on uncertainty as quickly as possible; that is, get to the 'killer experiment' (a pivotal experiment or experiments that resolve key uncertainty and generally result in a termination of development or significant increase in p(TS) depending on the outcome)
- maintain impartiality towards the success of the candidate ('truth seeking')
- defer investment in downstream activities that are not directly needed to determine the key clinical hypothesis until key risks have been discharged (that is, limit parallel processing)

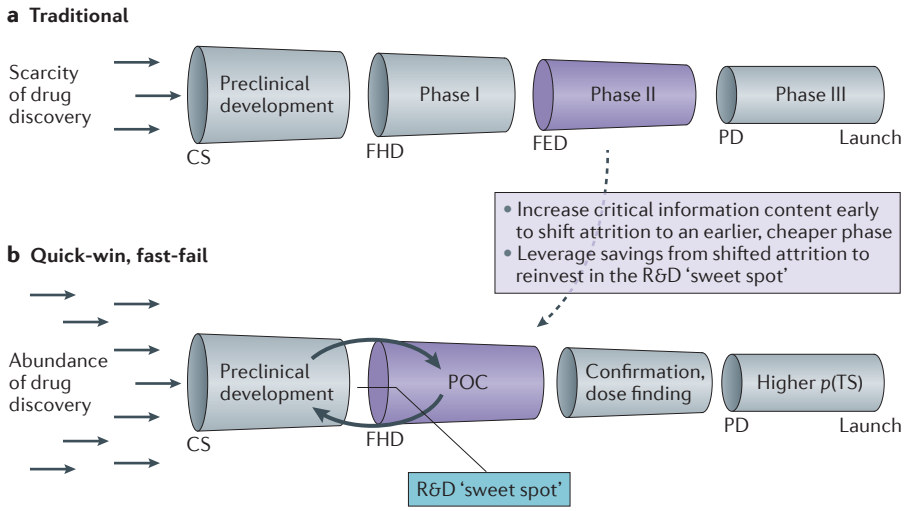


Figure 1 | **The quick-win, fast-fail model.** This figure illustrates the contrast between the traditional drug development model (part **a**) and an alternative, the quick-win, fast-fail model proposed by Paul *et al.*[2] (part **b**). In this alternative — with a greater focus on reaching proof-of-concept (POC) efficiently, faster and with lower cost — technical uncertainty is intentionally decreased before the expensive later development stages (Phase II and Phase III). The reduced number of new molecular entities entering Phase II and Phase III advance with a higher probability of technical success (*p*(TS)). Any savings gained from this paradigm can be reinvested to further enhance research and development (R&D) productivity. CS, candidate selection; FED, first efficacy dose; FHD, first human dose; PD, product decision.

- operate with a small, experienced and co-located internal team
- use a flat organizational model with all functions internal to Chorus (explained below)
- outsource work through a variable capacity management model (virtual R&D)
- operate on an efficient framework of phase-appropriate policies and standard operating procedures (SOPs), and embed a quality system to manage the flow of work
- use information technology (IT) for enterprise and project management
- minimize governance oversight
- allow independence in sourcing, procurement and contracting

Individually, each of these principles of efficiency can incrementally improve speed, cost and quality, but taken together they are synergistic and can create a transformational improvement in productivity.

Initial success led to the growth of Chorus staff, capabilities and portfolio. In 2005, manufacturing, toxicology, regulatory, quality and IT development staff were added to the initial medical and clinical operational capabilities. By 2008, definitive data packages and productivity metrics for the initial ten molecules had been returned to Lilly, the sponsor. At that time, Lilly declared that Chorus was no longer just a pilot programme but now an established alternative development path within Lilly Research Laboratories. Chorus was repositioned to service a portion of Lilly's active portfolio, and Lilly first described the Chorus group externally[6–8,11,12].

The Chorus model is differentiated in three main areas: development philosophy, organizational effectiveness and operational efficiency. This article describes each of these aspects of the Chorus model in greater detail and highlights the outcomes so far, which show how it has fulfilled the productivity-enhancing vision articulated by Paul *et al.*[2].

The Chorus development philosophy

Asset selection. Not every NME is an ideal candidate for Chorus L2POC development. Historically, Chorus and Lilly R&D leadership reviewed the Lilly portfolio with specific guidelines to select assets for Chorus L2POC versus traditional internal development (TABLE 1). In general, a 'lean' development approach is better suited to assets with a lower than typical *p*(TS) owing to lower target validation and/or identified resolvable risks. In simple terms, at a portfolio level, assets with a very low entry *p*(TS) would be much better pursued with L2POC development (if at all), as the most likely outcome is technical failure and this approach minimizes investment until the key risks are removed. By contrast, for assets with a very high entry *p*(TS), traditional at-risk development is warranted as the probability of technical failure is low and this approach maximizes speed to market and overall return.

Chorus assets are also selected on the basis of the ability to construct and execute an L2POC development plan to efficiently discharge risk at an early stage. The Chorus portfolio is not limited to specific indications or therapeutic areas; the philosophy is that efficient drug development is an expertise in and of itself. Specific medical and scientific expertise in a given therapeutic area, disease state and target can be accessed externally as needed. Chorus begins its consideration of an asset with a 'pharma-quality' candidate data package and a clearly defined target product profile; that is, a high-level strategic development intent articulated by the sponsor (indication, scope, proposed product attributes and differentiating features). For Lilly's internal assets (and more recently its external assets as well), Chorus conducts a preliminary review and planning exercise to determine whether an L2POC development approach is feasible. Rarely, if it is determined that there is no reasonable L2POC path, Chorus will decline the opportunity to work on an asset. More commonly, Chorus and the primary sponsor negotiate the high-level development strategy, including the proposed indication and target population, with the objective of finding a mutually agreeable L2POC path.

Constructing a lean plan: the central role of assessing proof of mechanism in Phase I. The non-clinical pharmacology data package often contains an experiment that demonstrates the key aspects of the intended pharmacological profile (for example, selectivity for one end point versus another, superior biomarker response to a key comparator drug, etc.) for which an analogous human experiment can be conducted in Phase I/Ib. The opportunity for this 'translational experiment' is frequently overlooked in pharmaceutical development, usually because the design, size or biomarkers are not viewed as statistically robust and/or validated. Although these concerns are legitimate, an equally valid viewpoint asserts that a drug is unlikely to achieve clinical efficacy in longer clinical trials if, in humans, it does not reproduce the pharmacology observed in short, small animal studies on which the value proposition of the asset has been built.

In these studies, drug–target engagement should be demonstrated using biomarkers of acute pharmacological response. The drug exposure needed to optimize this response should be described by the pharmacokinetic/

Table 1 | **Asset selection principles for the Chorus versus traditional model**

Chorus development	Traditional development
L2POC strategy	Fast to market strategy
Need to eliminate key risks for project before making a late-stage investment	Validated target or profile improvement
Have established biomarkers or clinical end points	Competitive area and internal commercial alignment
Can arrive at POC in <250 patients, therefore resulting in a change of *p*(TS) by ≥0.25 at a cost of ≤US$10 million	Disease state that requires large and long trials to demonstrate POC (for example, Alzheimer's disease and fracture prevention)
Focused indication	Multiple indications, therapeutic areas or geographies
Ideal for 'white space'; that is evaluation of non-core therapeutic areas	Deep internal development, regulatory and commercial experience

L2POC, lean-to-proof-of-concept; POC, proof of concept; *p*(TS), probability of technical success.

pharmacodynamic (PK/PD) relationship, which is often supported by modelling. The variability of the pharmacological response should be characterized in light of the apparent window between target engagement and safety limits (known as the therapeutic index). In some cases, a trial in a patient population with disease-related pathophysiology or longer durations of dosing may be necessary, and these should be included in the Phase I programme. In this manner, Chorus seeks to inform sponsors, before Phase II, whether adequate target engagement may be achieved with an acceptable therapeutic index, a practical dose regimen and a manageable degree of PK/PD variability. We refer to this as demonstration of proof of mechanism (POM).

Although rigorous statistical powering is difficult in small Phase I trials, sponsors should enforce attrition for drug candidates that are not acceptable in this regard. This concurs with the findings of Morgan *et al.*[13] in their retrospective review of Phase II programmes at Pfizer: "A key finding was that an integrated understanding of the fundamental PK/PD principles of exposure at the site of action, target binding and expression of functional pharmacological activity (termed together as the 'three pillars of survival') all determine the likelihood of candidate survival in Phase II trials and improve the chance of progression to Phase III" (REF. 13). Although an enriched Phase I data set focused on demonstrating POM is always scientifically satisfying, it is only worth the added cost and/or time if these data can influence decisions to modify the subsequent development path[13].

Although the assessment of POM in Phase I seems logical, it raises difficult questions about making development decisions on the basis of short-term biomarker studies. This question must be addressed on a case-specific basis. The experimental design, end points and dosing duration of the POM study should mimic the non-clinical pharmacology model to the greatest possible extent. If a relevant active comparator has a similar mechanism of action or has a convergent effect on a downstream biomarker, this should be incorporated into the POM study. Although PD markers in Phase I may not be suitable for definitive go/no-go decisions, they may be used for other development decisions. These may include dose selection for POC, the selection of minimalist (for example, single-dose-level and minimal special assessments) versus comprehensive (that is, dose-ranging, multiple end point assessments) approaches to the Phase IIa POC study, or decisions to trigger Phase IIb-related preparatory activities that are usually deferred in the L2POC paradigm. Chorus' approach to POM is shown in BOX 1.

Optimal design and implementation of the L2POC strategy. Not every asset gets to the stage of clinical POC implementation. As outlined above, some assets fail at the preclinical or POM stage. A central feature of the L2POC strategy is to pull risk forward and discharge it earlier, harvest the savings attributable to early attrition and re-deploy resources to more viable projects. For assets with favourable Phase I or POM data, clinical POC has emerged as an important development milestone owing to the crucial role of Phase II *p*(TS) in R&D productivity, as described by Paul *et al.*[2] and Cartwright *et al.*[14]. Simply put, improved Phase II *p*(TS) offers the greatest potential to increase the R&D productivity of any variable describing the drug development process.

Despite being widely discussed, it is difficult to define POC objectively. The intuitive appeal of rapidly showing a drug's key attributes in humans often resists consensus when the details of a POC experiment are proposed. Scientists naturally require a high level of 'proof', hold nuanced views of the 'concept' to be tested and often advocate for one or more definitive Phase II clinical trials before making any go/no-go decisions. Although understandable, this approach leads to the current unsustainable industry cost and cycle-time metrics. For POC to enhance the productivity of early-phase drug development, it must instead be defined as a demonstration of reasonable likelihood that key elements of efficacy and safety will be achieved[14] before definitive and expensive Phase IIb clinical trials are carried out.

Chorus and Lilly define POC as the first demonstration of the key aspects of the drug product profile in a patient population using clinical end points or surrogate markers. POC trials are meant to be filters, and thus unfavourable results must result in the termination or redirection of projects. This reality causes upset among specific molecule advocates, but when applied across a portfolio this process is a powerful tool for ensuring that projects advancing to Phase IIb have a higher-than-average *p*(TS) and drive improved R&D productivity. More recently, Chorus has used a formal decision-analytic approach to determine the optimal sequence of clinical studies. This approach, examining alternative development plan scenarios, is based on the dialogue decision process[15] in team-based decision making.

The optimal POC study must be tailored to the therapeutic area, disease state, target population and indication in light of the data that have already been developed and the remaining questions to be addressed. For some targets and assets with a good safety profile, with robust target engagement and biomarker data supporting dose selection, and with clinical or robust biomarker efficacy readouts, a simple two-arm study of the drug candidate at a single 'highest reasonable dose' versus placebo (or, if indicated, an active control) may be sufficient to definitively test the hypothesis. For other assets, considerably more complex studies may be required. In general, the POC study must be robust enough to support not only a determination of a reasonable likelihood of showing efficacy and safety but, importantly, also a reasonable likelihood that the asset should be terminated if the data are negative. The degree to which realistic Phase IIa studies can be designed to exclude false negatives based on rigorous classical statistics may be limited. A model-based or Bayesian approach may be more appropriate. Examination of all the data, including

concordance of the various safety and efficacy end points, is always necessary as is typical in the interpretation of Phase II data.

The greatest improvement in R&D productivity is realized when POC is achieved before investment in activities intended to support Phase IIb/III development (for example, long-term toxicology studies, commercial formulation development, chemical process definition and optimization, production of drug substance for Phase IIb and pivotal trials, definitive clinical dose-ranging studies, exploration of patient-tailoring strategies, etc.). In traditional development, with a speed-to-market mindset, this work is done at risk before any change in the initial *p*(TS). Furthermore, the cost of POC should be small relative to the cost of the definitive Phase IIb trial. This strategy to defer investment in all activities beyond an efficient POC study is an integral part of L2POC.

Although the L2POC strategy reduces the cost and cycle time to POC, limiting parallel processing poses a potential risk of delaying the subsequent development of projects for which a 'go' decision in favour of further downstream investment is ultimately made. For this reason, the wisdom of L2POC is debated. In order to minimize delays in cycle time due to L2POC, Chorus accelerates the testing of key project risks and communicates emerging data promptly to the sponsor and to the potential downstream developer. For the sponsor, this creates the option to make decisions to 'buy-up' initiation of Phase IIb/III-enabling investments based on emerging data. This data-driven acceleration of Phase IIb/III planning, combined with the inherent rapid cycle time to POC, can largely eliminate the potential delay associated with an L2POC development strategy for projects with a go-decision.

Chorus' approach to POC is shown in BOX 2. Although much of Chorus' work remains confidential, examples illustrating our approach to POM and POC have been published for projects with positive[16–18] and negative[19–21] outcomes with regard to supporting the subsequent progression of the programme, as well as for projects that are still active[22].

Organizational effectiveness

Chorus is able to sustain a portfolio of approximately 15–17 active projects in the 'candidate selection to POC' phase of development with approximately 40 full-time staff members. The fixed staff of Chorus are organized in a flat model, and comprise personnel with expertise in medicine, clinical pharmacology, patient safety, chemistry, manufacturing and controls (CMC), toxicology, pharmacokinetics, bioanalysis, asset project management, procurement, quality, IT, regulatory affairs and statistics. All personnel report through a single managing director who is accountable to Lilly for the overall operation. Historically, Chorus has sought out and used personnel with broad drug development backgrounds and multiple competencies for positions that are neither rigid nor 'siloed'. The result is a more compact, robust organization with lower business continuity risk. As a result of this staffing model, approximately 25% of the

Box 1 | **An example of a Chorus proof-of-mechanism study**

Background

LY2878735 is a new dual serotonin and noradrenaline transporter reuptake inhibitor (SNRI) that was in development for the treatment of chronic pain. The *in vitro* profile suggested a more balanced serotonin/noradrenaline transporter inhibition profile compared with other SNRIs, which was expected to confer superior clinical efficacy. Furthermore, LY2878735 had lower potential cytochrome P450 (CYP)-based drug–drug interactions. The IC_{50} (half-maximal inhibitory concentration) for inhibition of CYP2D6, CYP2C9, CYP1A2 and CYP3A4 was much larger than the serotonin- and noradrenaline-binding affinities, indicating low inhibition potential for these isoforms in humans, in comparison with the moderate CYP inhibition liability of venlafaxine and duloxetine. LY2878735 is metabolized partly by the genetically polymorphic CYP2D6 pathway, which raised pharmacokinetic variability concerns.

The Chorus development path for LY2878735 used a gated risk discharge approach: proof of mechanism (POM) followed by proof of concept (POC). First, the intended differentiating features of balanced dual pharmacology and the identified risks of pharmacokinetic variability and selectivity against common adverse effects in the drug class were to be assessed in a POM paradigm. Second, if POM was positive, efficacy and safety would have been evaluated in a POC study in a chronic pain indication. Phase I results have recently been published[19].

POM study design

Two incomplete crossover design Phase I studies were conducted in healthy volunteers using similar enrolment criteria and study end points. The first was a typical first-in-human single ascending dose (SAD) study. The second consisted of two parts; the first followed a typical multiple ascending dose (MAD) design, and the second evaluated serotonin occupancy using positron electron tomography. In the MAD study, dosing was once daily for up to 10 days. A total of 57 individuals participated in the studies. People who had poor CYP2D6 metabolism were specifically excluded from the SAD study, whereas the MAD study preferentially recruited people with poor CYP2D6 metabolism, resulting in 7 (25%) such individuals participating. Dense sampling was implemented for the study of pharmacokinetics, *ex vivo* noradrenaline and serotonin uptake inhibition, plasma noradrenaline and dihydroxyphenylglycol (DHPG), and blood pressure and heart rate. Sparser sampling was implemented for the study of serotonin occupancy to limit radiation exposure. Phase I pharmacokinetic and biomarker data were analysed by pharmacometric methods to characterize the balance between dual-target engagement and adverse effects on heart rate and blood pressure.

Results

LY2878735 seemed to be substantially more potent than duloxetine at noradrenaline engagement. The noradrenaline/serotonin potency ratio was ~1 for LY2878735 versus 9 for duloxetine. The relative potencies (the half-maximal effective concentration; EC_{50}) of the *ex vivo* serotonin and noradrenaline uptake inhibition measured in our clinical studies, 0.13 ng per ml and 0.71 ng per ml, result in a noradrenaline/serotonin potency ratio of 5 for LY2878735, compared with the reported value of 2.6 for duloxetine. Both results are generally consistent with the *in vitro* K_i (inhibition constant) ratios, where LY2878735 was shown to have fourfold higher serotonin-binding affinity compared with duloxetine and sevenfold higher noradrenaline-binding affinity. As such, LY2878735 is clearly more noradrenaline-favouring relative to serotonin as compared with duloxetine.

The LY2878735 concentration–response relationships for serotonin and DHPG suggested that only a narrow concentration window would offer a high percentage of serotonin and noradrenaline engagement without having clinically concerning effects on vital signs. The pharmacokinetics of LY2878735 appeared to be highly variable, further aggravating the narrow concentration-based margin of safety. CYP2D6 appeared to be the major pathway of clearance for LY2878735 and contributed to substantial pharmacokinetic variability. As compared with poor metabolizers, CYP2D6 extensive metabolizers have 21-fold higher clearance and threefold higher distribution volume. Even a CYP2D6-based dosing paradigm, explored through simulations, failed to support a comparable therapeutic index to duloxetine, a widely used SNRI.

Conclusion

Key differentiating features proposed for the molecule are unattainable, allowing a confident early termination decision.

Chorus budget is allocated to fixed overheads and approximately 75% allocated to external direct costs of asset development.

Throughout the time period covered, two to four senior-director-level physicians and clinical pharmacologists with considerable breadth of drug development expertise and experience have served as internal medical leadership at Chorus. With respect to qualifying, accessing and using external thought leaders, principal investigators, content experts, advisory boards, etc., Chorus' approaches are similar to those used in mainstream pharmaceutical development. Chorus uses the extensive connections of its senior medical leadership, as well as those of the sponsor, to establish and manage these relationships. In the collaborative process of developing the Chorus plan, internal experts in the relevant therapeutic areas provide sponsor input to the development plan. Most projects also use external expertise from thought leaders and principal investigators.

Upon entry of an asset into the Chorus portfolio, a two-person team is assigned to coordinate all planning and development activities. This team consists of the scientific leader (known as the asset manager) and the operations coordinator (known as the clinical research coordinator). The asset manager — a senior scientist with a Ph.D., Pharm.D. or M.D. who is experienced in early drug development and the design and implementation of clinical studies — is accountable for overall project leadership and management of the asset. The clinical research coordinator is an expert in clinical project management, vendor engagement and supervision, and study implementation. This two-person team is responsible for timelines and budgets, and engages other Chorus functional collaborators to design and oversee specific work modules within the plan.

Clinical research coordinators and asset managers can handle approximately three assets at any one time depending on the phase of development, number of clinical sites, geographic location, scientific complexity, etc. The two-person team and its collaborators (that is, CMC, toxicology, regulatory, PK/PD, statistics, quality, sourcing and medical representatives) assume a configuration of 'hub and spokes' to the wheel of project implementation. One of the key advantages of the Chorus model is that every two-person team is surrounded by essentially the same larger team of management and functional expertise to ensure cohesive cross-functional support and oversight. Furthermore, therapeutic or functional expertise that is not present in-house is accessed externally using a streamlined contracting process. The flat organization structure reporting up through a single line of management eliminates the function-team matrix dynamic, which slows decision-making. Finally, from its inception, Chorus outsourced all work using a variable-capacity management model with the goal of keeping the internal Chorus team small, experienced, co-located and under one management 'roof'.

In contrast to the standard pharmaceutical development model, this model ensures that a consistent team of experts works together on a regular basis, thereby building collective expertise in L2POC development. In this way, the matrix organization and hierarchical, function-based organizational design that is characteristic of large pharmaceutical companies has largely been eliminated. Chorus teams are also quite different from the small biotech or venture capital model in that Chorus has consistent staffing and a much wider range of in-house talent and quality control at its disposal, achieving scale efficiency. Overall, the goal has been to operate much like a nimble biotech while delivering work to pharma specifications.

Box 2 | **An example of a Chorus proof-of-concept study**

Background

LY2189102, a neutralizing interleukin-1β (IL-1β) monoclonal antibody, was already in clinical development for rheumatoid arthritis when literature reports of a marketed IL-1β peptide antagonist[28,29] and an investigational IL-1β monoclonal antibody[30] showed promising anti-diabetic results. These new data supported earlier reports that inflammation is associated with pancreatic β-cell apoptosis and reduced insulin sensitivity, and a previous Phase I programme with LY2189102 had shown a robust effect on inflammatory markers, providing a proof of mechanism. Chorus was charged with assessing the potential for LY2189102 as an anti-diabetic agent, for which Chorus devised a proof-of-concept Phase IIa study. There were two critical success factors for LY2189102: a statistically significant haemoglobin A1c (HbA1c) reduction, conducive of a long-term clinically meaningful magnitude based on a dynamic model of HbA1c, and a statistically significant reduction in high-sensitivity C-reactive protein (hsCRP). The study also aimed to generate, with minimal additional investment, a data set rich enough to conduct exploratory subpopulation analyses and exposure–response modelling to aid the design of a subsequent Phase II study.

Study design and methods

The study was a randomized, double-blind, parallel, placebo-controlled trial of subcutaneous LY2189102 (0.6, 18 and 180 mg) administered weekly for 12 weeks in patients with type 2 diabetes; this group was enriched for higher inflammation status (elevated baseline hsCRP >2.0 mg per dl) and an HbA1c between 7.0% and 10.0% on diet and exercise, with or without approved anti-diabetic medications. A total of 106 patients were randomized and comprised the full analysis set. The compliant set included 79 patients, 23 of whom received placebo, 21 patients received 0.6 mg of LY2189102, 16 received 18 mg of LY2189102, and 19 received 180 mg of LY2189102.

Results

LY2189102 was well tolerated at all doses, and reduced HbA1c at 12 weeks (adjusted mean differences versus placebo: −0.27%, −0.38% and −0.25% for 0.6 mg, 18 mg and 180 mg doses, respectively). LY2189102 also reduced fasting and postprandial glycaemia, as well as inflammatory biomarkers, including hsCRP and IL-6. Changes from the baseline in both fasting glucose and HbA1c appeared to correlate weakly with baseline hsCRP, such that higher starting hsCRP serum concentration was associated with an improved glycaemic response at the end of dosing.

Conclusions

Although statistically significant, the effect of LY2189102 on HbA1c did not meet the desired magnitude, resulting in a termination of the original scope of development[20,21].

Operational efficiency

How Chorus operates. At the outset of a project, the asset manager and clinical research coordinator orchestrate a comprehensive planning exercise that includes all of Chorus' technical functions and external consultants. This exercise begins before the acceptance and entry of the project into the portfolio, ultimately culminating in the final development plan. The development scientists (toxicology, medical, PK/PD, drug metabolism, etc.) assess key uncertainties and create study concepts to address these unknowns. In parallel, the CMC team develops an early-phase, fit-for-purpose clinical trial material (CTM) supply strategy to support the research plan. Each module of proposed work is shaped not just by scientific objectives but also by the feasibility of implementation, opportunities for strategic sourcing of vendors and optimization of cost and cycle time.

With a suitable asset and approach to development in hand, Chorus team members design specific modules of work, consisting of one or few experiments, to discharge

addressable risks and to estimate the cost and timing required. Some projects have CMC, drug metabolism, toxicology and clinical requirements that pose higher-than-average uncertainty. Examples may include suboptimal biopharmaceutical properties, a toxicity signal from pilot studies, mechanism-based safety concerns or the need to show differentiation with respect to a specific comparator. Chorus explicitly investigates these potential weak points as early as possible.

Clinical efficacy is typically a key uncertainty. The approach for assessing POC through biomarkers or clinical end points in Phase I or Phase IIa varies greatly depending on the indication. Some clinical efficacy and safety risks are not resolvable in Phase IIa, and these remain out of scope. The L2POC approach focuses the plan on the modules of work with the highest information value, seeking to maximize the resulting change in the *p*(TS) in the shortest time and at the lowest cost. The amount of risk discharged and the information delivered must be sufficient to support a declaration of POM or POC and the associated investment decision.

The information value within a module of work represents the key uncertainties to be resolved, with a focus on the experimental unknown to be explored, the methods by which to measure results, and the critical success factor (CSF). The CSF for a module is typically quantitative and specifies the minimum essential criteria for continued development. A well-crafted CSF is one that allows for a definite conclusion on whether the results meet the CSF without ambiguity. Imprecise statements such as 'positive signal of efficacy', 'no adverse toxicology findings' or 'adequate absorption, distribution, metabolism and excretion (ADME) properties' often disguise uncertainty or lack of consensus among key stakeholders. By contrast, specificity in CSF phrasing often triggers the resolution of these strategic ambiguities at an earlier stage of development, and thus facilitates proper design of the most efficient pathway and 'killer experiment' to address the key uncertainties. For each CSF there is a possibility of a 'borderline' result, where a rigorous binary approach is inappropriate. Despite this, giving prior thought to the possible range of borderline results and how decisions will be made in these cases is a very useful exercise. Chorus adds intangible value by impartially driving this clarity in the planning process.

Early in its evolution, Chorus learned that innovative clinical and CMC strategies may fail if key members of operations, sourcing, regulatory affairs and quality are not engaged throughout the entire process. To counteract this, clinical plans are reviewed in draft form in asset-review sessions. These review sessions involve all the functions supporting the core asset manager and clinical research coordinator duo, as well as Chorus management. In this forum, the integrated development plan is finalized. With all the relevant decision-makers involved, functional reviews and re-planning — which are common in a large organization — are avoided. At the level of an individual study, the asset manager develops protocols with suitable input from internal and external medical content experts as well as clinical operations. Direct involvement of medical and operational leadership ensures that the scientific, medical and operational plan is sound. The protocol is then subject to a scientific protocol review committee chaired by the Chorus Chief Medical Officer and a final operational review chaired by the Chorus Chief Operating Officer.

After the integrated plan is finalized, specific technical collaborators work with the two-person team to deliver work modules that support the clinical studies (for example, toxicology studies, assay validation, CTM supply, clinical protocols, regulatory documents, results, etc.). The Chorus functional expert oversees the vendor's work activity and keeps the asset manager and clinical research coordinator informed of progress. To a large degree, project management of the module of work is left with the functional collaborator who designed the module and who is accountable for its delivery. As results emerge, they are reviewed promptly with team members and management. The asset manager and clinical research coordinator can conduct the Chorus development plan largely without regular team meetings or committee reviews provided there are no influential new data or external factors.

In early clinical development, emerging data often indicate that a modification in development strategy or plans is necessary. The opportunity to learn from emerging data and modify plans as they evolve is embraced as a key capability. Chorus is well suited, as a flexible organization, to operate in this translational development capacity.

Governance. Another differentiating feature of Chorus development is 'arm's length' governance. Although Chorus operates as a part of Lilly, the only mandatory reviews of Chorus' projects by Lilly's governance are as follows: at the onset of the project, there is a review of the overall plan, timeline, budget, CSFs and final deliverables. Before any first-in-human study, there is a review of the good laboratory practice (GLP) toxicology data and risk management plan, and there is a review following the presentation of POM or POC data for assessment. The sponsor, not Chorus, makes the final assesment of whether the pre-specified CSFs defining a positive POM or POC have been met.

Typically, Chorus will review emerging data with the primary internal asset sponsor upon completion of GLP toxicology, end-of-Phase I or POM, or at any point at which emerging data indicate that a change in plan may be warranted. During informal check-ins with the sponsor, there are rarely any differences of opinion in how or whether to proceed, which is a reflection of the detailed development plan and the collaborative nature of the relationship. If differences do occur, then Chorus works with the sponsor to arrive at a mutually agreeable path forward; however, it is the sponsor that has the final say and responsibility for the overall development strategy.

Sourcing, procurement and contracting. In contrast to many large pharmaceutical companies that establish preferred and strategic supplier relationships, Chorus forms contracts with the supplier it deems best suited to the project's requirements. Chorus can qualify vendors, as well as negotiate and execute vendor agreements in order to gain efficiency by placing work with best-performing vendors. Chorus generally allows qualified service providers to follow their own standard operating procedures (SOPs) for work — provided such SOPs concur with appropriate regulations and sponsor requirements. This model allows Chorus to accommodate a wide variety of studies and methodologies, as the procedures that are required to implement the work are owned by the provider, which allows more efficient use of SOPs that are already familiar to the provider and not dictated by Chorus.

CMC. Chorus' CMC group is a key source of efficiency in the Chorus model. Chorus develops a route for good manufacturing practice (GMP) drug substance production that is appropriate to the scale required for early development. Typically, Chorus' CMC group supervises the manufacture of drug substances and drug products for small molecules and oligopeptides. Historically, Lilly has supplied drug substances for engineered proteins and antibodies, but Chorus has now developed the ability to provide these by contract manufacturing as well. Formulation development is limited to the most cost-effective strategy that is suited to the biopharmaceutical properties of the candidate and the needs of toxicology

and early clinical trials. Solutions, suspensions, drug-in-capsules, simple dry blends as well as enhanced formulations (such as a solid dispersion) have all been adopted when appropriate to support clinical studies.

The costs and benefits of alternative manufacturing scales and drug delivery options (parenteral, extemporaneous preparations, oral solutions for inpatient dosing, tablets for outpatient administration, etc.) are considered during the initial development of the scientific strategy. All drug substance synthesis and study drug manufacture is conducted with third-party partners. For each project, a single Chorus CMC scientist is responsible for drug substance, drug product, analytical controls, assembly of the regulatory dossier and supervision of both development and manufacturing. This model eliminates the multiple interfaces that normally exist in manufacturing and establishes clear lines of accountability for the delivery of materials. A different CMC staff member manages CTM. This role oversees packaging, labelling, distribution to clinical sites, monitoring at sites and also includes CTM disposition to ensure sponsor oversight throughout the entire clinical process.

Information technology. A key tool that permits a streamlined planning and execution process is Chorus' proprietary project management software system. This secure system, called VoiceNET, is used to track and monitor the entire Chorus portfolio, comprising both internal and external sponsors, with the ability to track data and documentation for individual molecules from external suppliers, contracts, procurement and financial elements. It also hosts the Chorus quality control system and is fully compliant with Part 11 of Title 21 of the US Code of Federal Regulations (CFR) for electronic records and electronic signatures. It was developed using a lean approach independently of Lilly's internal systems by a well-recognized external contract IT provider with specifications designed by Chorus individuals. Over time, the system has continued to evolve, most notably in its ability to interface with Lilly's internal system. It is currently managed by a global IT solutions provider, and has been audited by Lilly's internal IT and quality assurance (QA) groups.

Quality. Chorus writes, maintains and operates on its own phase-appropriate SOPs, as well as Chorus-specific business processes covering preclinical studies, clinical operations, GMP, sourcing, procurement and contracting. The SOPs are constructed to embed the Chorus quality control system into the flow of outsourced work. These Chorus SOPs, business processes and the quality system are aligned with the Lilly Global Quality System and conform to all appropriate regulatory, legal, medical, ethical and global business standards.

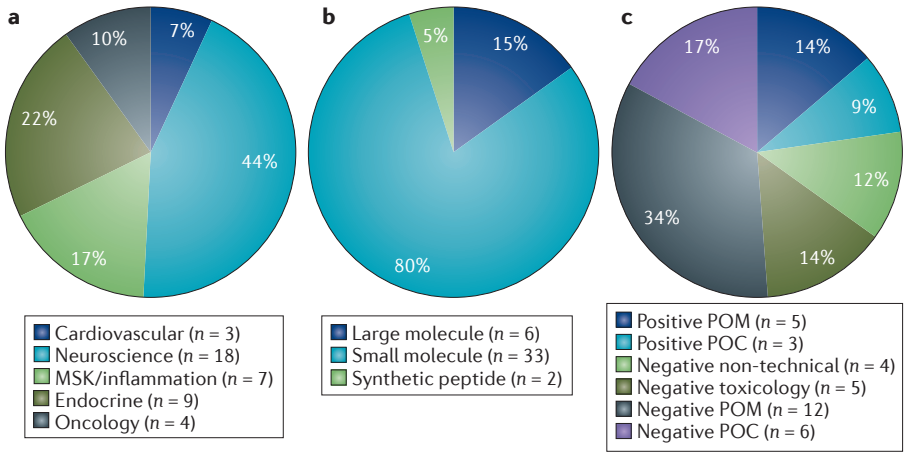


Figure 2 | **Summary of characteristics of the Chorus portfolio.** The Chorus portfolio has included 41 molecules distributed across five therapeutic areas (part **a**) and three molecule types (part **b**). Of the 35 completed programmes (part **c**), 23% have had a positive outcome, with negative outcomes reached across three specific technical attrition points. MSK, musculoskeletal; POC, proof of concept; POM, proof of mechanism.

The Chorus remit and results to date

As a division of a large pharmaceutical company, Chorus has enjoyed a steady flow of high-quality drug candidates that has enabled it to operate at optimum size and efficiency. A key aspect of its efficiency is the restricted scope of work from candidate selection to clinical POC (Phase IIa). Chorus does not perform medicinal chemistry, ADME or other elements of lead optimization to select a specific drug candidate. In cases where there are deficiencies in the non-clinical or biopharmaceutical data package, Chorus has negotiated with the sponsor to remedy these or find external vendors to do so. Chorus also does not perform detailed long-range commercial or registration-phase planning, nor does it design or implement pivotal trials.

Comparable to any similarly sized function in a large pharmaceutical company, Chorus' costs are accounted for on a full-time equivalent (FTE) basis and include business infrastructure, human resources, corporate IT, legal, security and physical infrastructure maintenance, which are all provided by Lilly. The description of outcomes and metrics here focuses on Chorus from its inception in 2002 through to 2012. It excludes those assets, both internally and externally discovered, that have been funded by external sponsors in the last 2 years ($n = 5$). The scope of work for Chorus has evolved over the years. Before 2006, Chorus obtained assets for which drug substance synthesis and toxicology studies were underway; thus Chorus' CMC group focused primarily on drug product work and Chorus toxicologists supervised the completion of an investigational new drug (IND)- or clinical trial application (CTA)-enabling package. Since 2006, Chorus has acquired the majority of its assets at candidate selection, before the first major drug substance synthesis and pilot toxicology studies, and it has adapted to support this full-scope 'candidate selection to POC' work in diverse therapeutic areas. Similarly, in the clinical phase, pre-2006 Chorus assets often required a single 'killer experiment' before asset transfer back to Lilly for continued development. In recent years, however, Chorus has designed and implemented clinical trials spanning Phase I to Phase IIb, including complex development paths (for example, oncology) and robust larger Phase II POC studies.

Through 2012, excluding the five externally financed projects, the Chorus portfolio has included 41 molecules. The clinical work was conducted globally in a total of 19 countries, and the majority of these studies were conducted outside the United States. FIGURE 2 outlines how the portfolio has been distributed across five therapeutic areas (FIG. 2a) and molecule types (FIG. 2b) including small molecules, synthetic peptides and large molecules. Of the 35 completed programmes (FIG. 2c), 23% have had a positive outcome, 5 reached a positive POM and 3 reached a positive POC. Of the 27 (77%) programmes

with a negative outcome, that result was reached based on toxicology data ($n = 5$), based on Phase I or POM clinical evaluation ($n = 12$), after a negative POC clinical trial in patients ($n = 6$) or the programmes were terminated for non-technical reasons ($n = 4$).

Since 2007, when Chorus first communicated early-stage cycle time and development costs to both internal (Lilly) and external audiences[6,7], performance metrics have been the one facet of the Chorus story that has attracted the most attention. The attractive performance data were often critiqued when any attempt at comparative analysis to internal metrics was performed. We have long agreed with the critique that any direct comparison of Chorus data with published pharmaceutical drug R&D costs is an 'apples to oranges' comparison, with respect to the fact that the sequence and scope of the work conducted is different. Traditional pharmaceutical drug R&D cycle time and costs to get a molecule from candidate selection through Phase II are approximately 48 months and US$42 million[2,23,24], respectively, and these figures are based on a development platform that is quite different to that of Chorus. These time and cost metrics also assume that POC occurs at the end of a robust Phase II study essentially coincident with the decision to initiate commercialization and registration studies. For assets that are suitable for L2POC, the Chorus approach takes the programme to an earlier investment decision in a shorter time and at a substantially lower cost — 28 months and ≈$6.3 million — than the more definitive Phase IIb decision point in the conventional R&D model.

Although it is extremely difficult to interpret development cycle times in early-phase drug development as each programme is very different, we provide a broad overview of our historical data as a measure of operational efficiency. Chorus cycle-time data for programmes that entered the portfolio are shown in FIG. 3a. For all 41 Lilly-funded Chorus programmes to date (these include the 35 exited programmes and the current 6 active internally funded programmes using forecasted data), the median number of days those programmes resided in Chorus was 772 (and the mean was 838). Broken down further, programmes that exited did so after a median of 331, 776 and 886 days as a result of definitive toxicology, clinical POM and clinical POC data, respectively.

The current portfolio of six internally funded programmes is experiencing a markedly higher cycle time, with a projected median time of residence in Chorus of 1,605 days. This is not a reflection of reduced productivity, but is instead due to a smaller number of internal projects, many of which involve larger Phase II studies. In recent years, Chorus has undertaken several projects that lack early POM or POC decision points and involve difficult-to-recruit populations (for example, cancer and chronic kidney disease). Although Chorus is capable of developing any asset through Phase II, the group was designed and is best deployed to manage assets that are amenable to 'lean-to-proof-of-mechanism' (L2POM) or L2POC development. For assets that are not well suited to this approach, Chorus' operational efficiency is still realized; however, more recent results support the proposition that the L2POM/L2POC development strategy is a larger contributor to improvement in productivity than operational efficiency.

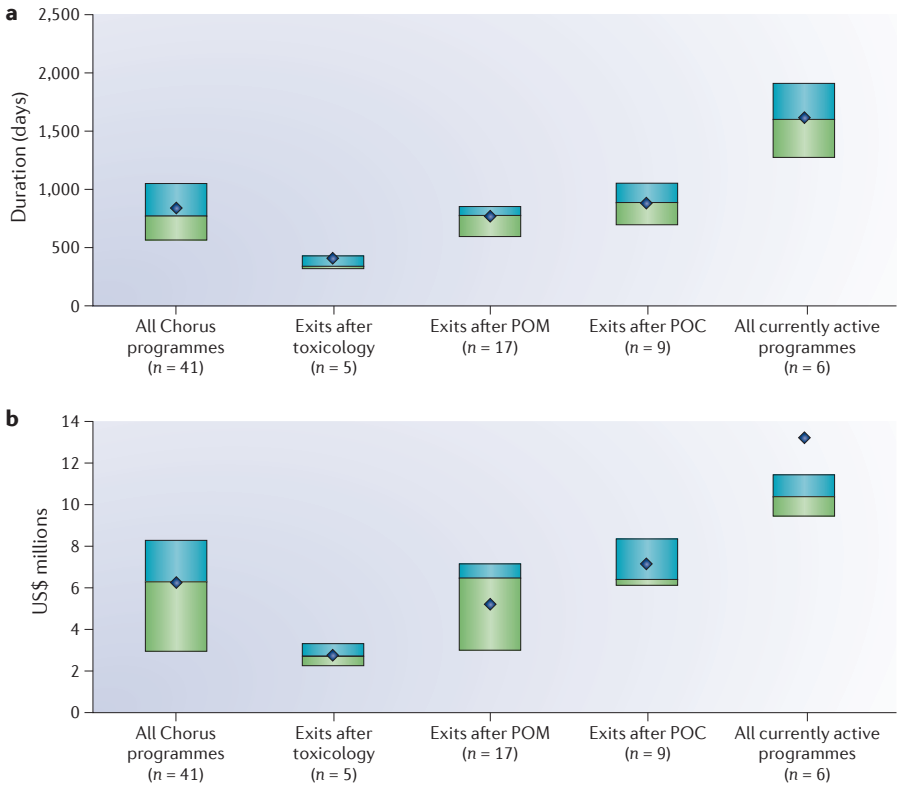


Figure 3 | **Time and cost of Chorus programmes.** The figure shows the total duration of drug development in days (part **a**) and the total out-of-pocket costs (part **b**) for Chorus programmes. The data shown are for all internally funded Chorus programmes to date ($n = 41$), which are then broken down into programmes that have exited Chorus before clinical trials ($n = 5$), after proof of mechanism (POM; $n = 17$) or after proof of concept (POC; $n = 9$). For the currently active portfolio ($n = 6$), durations represent the total duration to date plus projected time to exit, and costs represent total out-of-pocket costs incurred to date plus projected total costs. In each case, the total box represents 50% of the data set, with the lower box (green) representing the second quartile to the median value and the upper box (blue) representing the median value to the third quartile. Mean values are shown with blue diamonds. The programmes that exited owing to non-technical attrition ($n = 4$) are not represented. Total out-of-pocket costs are defined as the 'direct' contracted costs for the execution of work at third-party external providers plus the 'indirect' Chorus administrative costs (salaries, travel, etc.) calculated at a 10-year historical average of 24.7%.

Every one of the 35 exited programmes entered and exited Chorus with differing complexities. For most programmes some level of manufacturing or toxicology work had to be completed by Chorus; some had a single clinical trial, whereas others had as many as three. What can be concluded, however, is that each programme entered the portfolio with a development issue or question to be addressed and each exited with a definitive decision to enable the next development step. A deeper view of cycle times for programmes requiring the full scope of 'candidate selection to POC' work in Chorus can allow evaluation of the times between milestones. The Chorus median number of days for completed projects between first toxicology dose (FTD), first human dose (FHD) and first efficacy dose (FED) is 291 for

FTD–FHD ($n = 15$) and 296 for FHD–FED ($n = 9$). These cycle-time data compare very favourably against equivalent pharmaceutical composite industry cycle-time data and translate to favourable programme costs.

Similar to cycle-time comparisons, the interpretation of development costs in early-phase drug development is challenging as each programme is very different; however, we can still provide a broad overview of our historical data as a measure of operational cost efficiency. Chorus' total out-of-pocket cost data for all programmes that entered the portfolio are shown in FIG. 3b. Total out-of-pocket costs are defined as the direct contracted costs for the execution of work at third-party external providers plus the indirect Chorus administrative costs (salaries, travel, etc.) calculated at a 10-year historical average of 24.7%. The median total development cost for the programmes run in Chorus to date ($n = 41$) is $6.3 million (and the mean cost is $6.3 million). An important caveat to these data is that approximately 20% of the Chorus projects involve large molecules (monoclonal antibodies and engineered proteins). For these projects, Chorus was supplied with drug substances by Lilly, and the appreciable cost of manufacture is not reflected here. We have analysed this number in several ways: by eliminating early programmes that did not require manufacturing or toxicology work, by removing programmes that had expensive large-molecule manufacturing costs, and by only including programmes that had clinical trials; however, in each comparison, the median value did not appreciably deviate from the Chorus overall median value. The costs do deviate, however, from all historical Chorus median values when only the current programme median values of $10.3 million ($n = 6$) are considered, for the reasons described above.

It is important to note that the nature of the current Chorus portfolio no longer reflects the historical portfolio, as over 50% of the current portfolio is in large Phase II programmes. This recent experience supports the assertion that, even with an efficient operational platform, cost and cycle-time metrics are dependent on finding opportunities for early POM or POC decisions. The development of assets that lack these opportunities contributes to reduced portfolio performance, even in the L2POC paradigm. This is illustrated in FIG. 4, which outlines the historical nature of the Chorus portfolio. Each programme is numbered as it entered the portfolio, and key information on the programme can be obtained from this figure, such as programme flow,

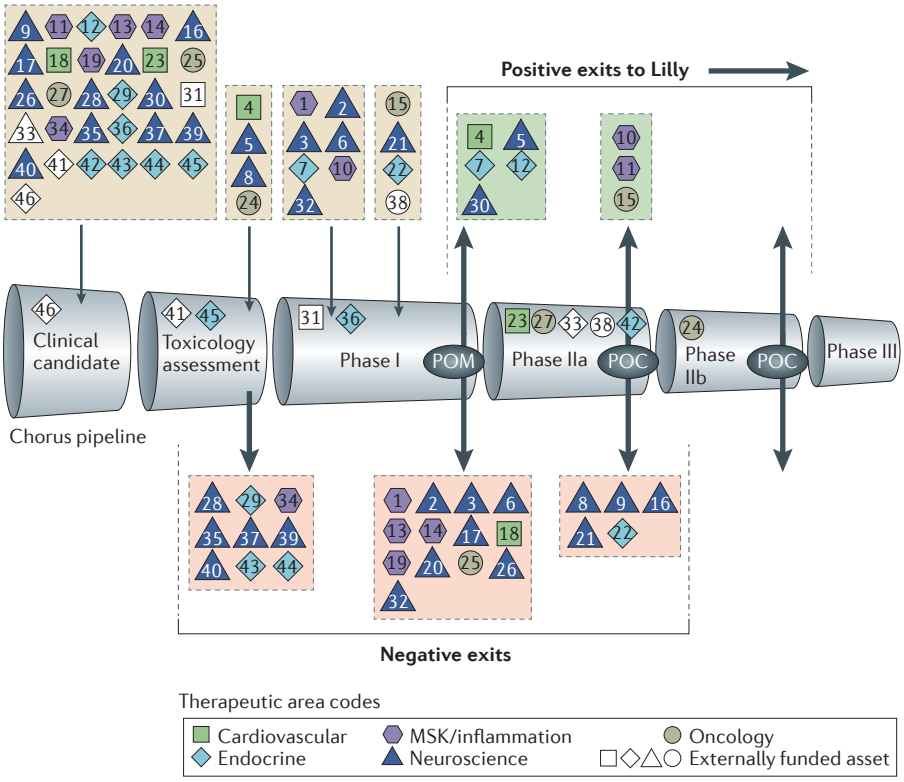


Figure 4 | **Ten years of portfolio flow through Chorus.** Each molecule is represented as a number and listed in the order in which it entered the Chorus portfolio. Each molecule is categorized by therapeutic area and whether it was funded by Lilly (the default) or by an external funding source (shown without colour shading). The phase of development at which each molecule entered the portfolio is represented at the top and where it exited as a negative development decision at the bottom. Positive exits are shown returning to the internal Lilly portfolio after either a positive proof of mechanism (POM) or proof of concept (POC). There is one current oncology asset in Phase IIb clinical studies. The current portfolio of 11 programmes (6 internally funded and 5 externally funded) is shown within the diagram, highlighting the number of active Phase II programmes currently being pursued. MSK, musculoskeletal.

development duration, therapeutic area, points of entry, points of exit, positive and negative outcomes and whether they were internally funded (that is, by Lilly) versus externally funded. One can see that over time the therapeutic focus for the Chorus portfolio has shifted, as has the number of larger Phase II trials.

The results described above are a historical review of Chorus' portfolio metrics and provide a measure of operational efficiency. However, most readers are seeking to understand whether drug development utilizing the Chorus L2POC model improves the overall productivity of pharmaceutical R&D compared with traditional drug development. Since the very beginning, the primary critique of the Chorus L2POC strategy of limiting parallel processing has been the potential downstream costs of development delays leading to potential revenue loss for successful projects. This critique has been formulated in many ways but can be summarized generally as: 'any delay in launch will cost a billion dollars per year in lost revenue'.

In the absence of a well-controlled R&D productivity comparison between the Chorus L2POC and the traditional model, we attempted to answer these lingering questions using financial modelling. We have therefore built a financial model that incorporates the operational cost, duration and the probability of transitioning from one stage of development to the next. The beginning time point in the model is candidate selection, representing the end of lead optimization, a common point of entry for traditional and L2POC models. Essentially, the model compares the development path of a typical Chorus molecule had it been developed simultaneously in the traditional and Chorus L2POC models. Details of the analysis, assumptions and findings are

described in BOX 3 and TABLE 2. We believe that these analyses show marked improvements in development cost with the Chorus L2POC model and provide clear evidence to refute the decade-long myth that the Chorus L2POC strategy of limited parallel processing creates value in the short term only to destroy value in the long term for programmes that are successful in reaching the market.

Challenges and opportunities

The L2POC model in large pharmaceutical companies. The optimal sponsor of L2POC needs both a robust candidate discovery capability and a portfolio management

Box 3 | Does the Chorus L2POC strategy make economic sense?

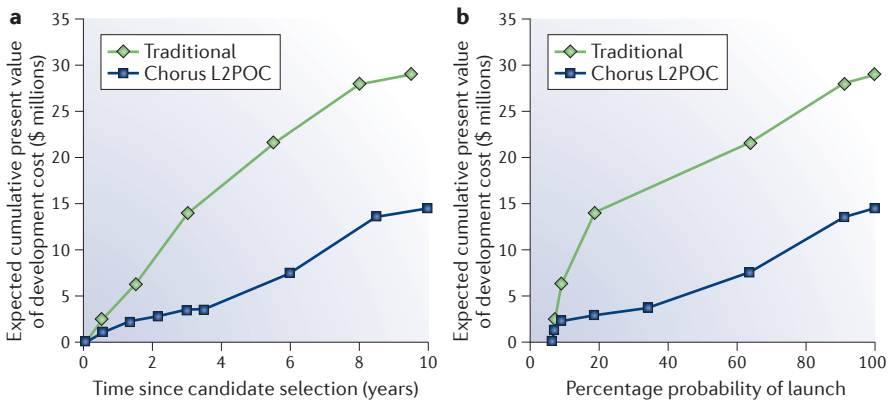
To address whether the Chorus lean-to-proof-of-concept (L2POC) strategy provides cost savings in the short term, but destroys value in the long term owing to delays to market for successful projects, we built a financial model using assumptions of operational cost, cycle time and attrition rates for traditional development from Paul *et al.*[2]. Minor modifications were necessary to address the question. First, attrition rates were increased to represent the higher-than-average risk associated with Chorus-type projects of high target novelty or notable starting risk, which typically excludes line extensions and new indications for existing products. Furthermore, we created two new stages to reflect the L2POC model: candidate selection to first toxicology dose (FTD), and first human dose (FHD) to proof of concept (POC). We also used the estimates of stage-specific development cost and cycle-time durations from Paul *et al.*[2] to represent the traditional development model. For the Chorus L2POC assumptions, we used actual average Chorus total operational development costs and cycle-time durations for relevant stages of development. To maintain a fair comparison, the attrition rates were assumed to be the same regardless of the development model, as these are a property of the molecule in development. The key difference is that the L2POC model creates a POC milestone in Phase II. We assumed, conservatively, that the activities in Phase II before POC resolve similar magnitude of risk compared to activities after POC. The assumptions on cost, cycle time and probability of technical success are summarized in TABLE 2.

The financial model accounts for two important elements of drug development: namely, the time value of money and the probability of technical success (*p*(TS)). The time value of money reflects the opportunity cost by discounting future funds by the cost of capital: the annual rate of return expected by investors based on the level of risk of that investment. We used an 11% cost of capital as Paul *et al.*[2], which is a reasonable long-term assumption. Given the long drug-development times (10+ years), the time value of money is one of the most crucial — but arguably the most underappreciated — factors in any financial analysis considering drug development costs and revenues. Capitalizing future streams of money reflects them in present time value, allowing a comparison across different time profiles of expenditure or revenue. Second, we operate in a very high-risk, high-attrition business. Most future events, including expenses and projected revenue generation, simply never occur. In our model, all operational costs are 'probabilized'; that is, simply adjusted for *p*(TS) using the archetypical values noted above to represent the expected incurred costs or acquired revenue in the life of a project. We believe that capitalizing and probabilizing future streams of drug development costs allows a more direct comparison of the Chorus L2POC and traditional model as viewed from the decision-maker's perspective at the point of candidate selection when a development paradigm is chosen.

The output of the financial model, shown in the figure, provides a comparison between the traditional and Chorus L2POC development models. The cumulative expected (probability-adjusted) and capitalized (present value) cost of development is displayed as a function of both development time and the probability of launch. As the L2POC model limits large investments until after a substantial risk has been resolved (after POC), the expected L2POC present value of the operational cost shows a marked difference from traditional development, largely driven by avoiding Phase II development costs for failed projects. The expensive full Phase II programme is conducted for only 18% of projects in the L2POC model, but for 34% of projects in the traditional development model. Given the large and early cost of Phase II, the difference is notable, resulting in approximately 61% and 45% lower expected capitalized development cost to first registration dose (Phase III) and launch, respectively. Paul *et al.*[2] found that *p*(TS) in Phase II is the biggest driver of the capitalized cost per launch, and therefore a strategy that removes a substantial portion of that Phase II risk at a low cost — that is, L2POC — obviously results in a large overall saving.

To more accurately address the primary critique of the Chorus L2POC strategy of limiting parallel processing and the consequent potential downstream cost in the form of potential revenue loss, we conducted a sensitivity analysis across a 0–24-month launch delay for a molecule developed in the L2POC model. Development delays were simulated to occur after POC before completing a typical Phase II programme. We assumed 5-year peak annual sales of US$1 billion with linear accrual, with 8 years of total exclusivity, and a 1-year linear ramp-down of revenue to zero after the loss of exclusivity. Overall probability of launch (6%), duration of development (9.5 years) and an 11% cost of capital rate are derived from TABLE 2. With these assumptions, the present value of total revenues from that $1 billion drug, on a probability-adjusted basis, is merely $62.5 million. This emphasizes the crucial importance of the following three factors on drug development costs: high attrition rates, long cycle times, and the large effect of the time value of money.

In our analysis, any launch delay was assumed to shorten the duration of peak sales in the same delay magnitude. Thus, a launch delay of 1 year would result in a $1 billion revenue loss, which corresponds to a $10.1 million loss on an expected present value basis. The expected present value of the net effect of a launch delay — that is, the savings in development costs minus the loss of revenue — range from a $13.1 million net gain for a 0 month delay to a $6 million net loss for a 24-month delay, with a break-even point of a 16-month delay based on our financial assumptions. Thus, it is financially more prudent to adopt an L2POC model for molecules in development with the assumption that once, and if, a POC can be shown, a delay of no more than 16 months can be tolerated.



perspective that is focused on the discontinuation of development for unpromising assets and re-deployment of resources to more productive projects at the portfolio level. Given this, a fully integrated pharmaceutical company is best positioned to sponsor L2POC, and Chorus' strategic integration with Lilly has enabled Chorus to achieve its R&D productivity metrics with a reliability and quality that small biotech organizations are unlikely to achieve.

Despite this fit and the favourable metrics, why are there few — if any — replicas of Chorus in the pharmaceutical industry? Conceptually, the Chorus model is challenged by two contradictory beliefs within large pharmaceutical companies: first, that the L2POC approach poses undue risk in drug development owing to 'leanness' and, second, that the functional matrix organization can do L2POC just as well, without radical redesign. With regards to the 'risk' associated with L2POC development, the concern is that deferred investment — that is, limiting parallel processing — slows the overall time to launch, erodes patent life and reduces the value of the asset compared with the more expensive traditional, at-risk model assuming success. This concern is addressed above and in BOX 3, and we consider it to be unfounded. Chorus' early clinical development success rate (23%) is similar to pharmaceutical industry metrics, which suggests that false-negative rates are not higher in the Chorus model of development. Failure rates are similar to the industry level overall, but realized at lower cost owing to 'lean' investment and earlier project terminations. The belief that a large functional matrix organization can achieve Chorus-like metrics by adopting elements of a lean development approach ignores the synergy that is achievable when the entire package of Chorus-founding principles is embraced.

In many ways, for the traditional pharmaceutical company, Chorus represents a disruptive business model as described in the business classic *The Innovator's Dilemma*[25]. Indeed, as Christensen observes: "With a few exceptions, the only instances in which mainstream firms have successfully established a timely position in a disruptive technology were those in which the firms' managers set up an autonomous organization charged with building a new and independent business around the disruptive technology." This is, in fact, exactly what Lilly did when Chorus was established. Reorganizing pharmaceutical R&D into more manageable units would be needed to fully internalize the Chorus approach to development. There has been a growing recognition that "to save themselves, pharmaceutical companies will have to break up their giant R&D organizations, overhaul core processes and put their passionate scientists back to work" (REF. 26). Unfortunately, efforts to date have focused more on reorganization rather than fundamental transformation of the R&D enterprise; however, as pharmaceutical companies struggle to create innovative medicines with manageable levels of R&D investment, the need for productivity gains may overcome organizational resistance to change.

Although Chorus has not been fully reproduced internally in another large pharmaceutical company, several pharmaceutical companies have embraced parts of the model, particularly the small, relatively autonomous, virtual team structures; the Centre for Excellence for Drug Discovery (CEDD) and discovery performance unit (DPU) concepts at GlaxoSmithKline, iMED groups at AstraZeneca, Pfizer's Neusentis and the external development group (EDG) at Roche are a few examples. Time will tell, however, whether these 'sponsor-captive' development groups can adopt the agnostic perspective and discipline required to drive early attrition, which is necessary for realizing the transformational productivity improvements that Chorus obtained.

Adoption of L2POC by other drug development organizations. The challenge of promoting the Chorus model within big pharma raises the question of whether other types of organizations could use the Chorus approach. Apart from large pharmaceutical companies, few organizations engaged in

Table 2 | **Parameters for economic model comparing Chorus L2POC strategy to traditional strategy**

Variable	Development model	Preclinical		Phase I	Phase II		Phase III	Submission	Combined
		CS–FTD	*FTD–FHD*	*FHD–FED*	*FED–POC*	*POC–FRD*	*FRD–FS*	*FS–FL*	
p(TS)	Traditional	90%	77%	49%	29%	–	70%	91%	6%
	Chorus L2POC	90%	77%	49%	54%‖	54%‖	70%	91%	6%
Cycle time (years)	Traditional	0.5	1.0	1.5	2.5	–	2.5	1.5	9.5
	Chorus L2POC	0.5	0.8	0.8	0.8	2.5	2.5	1.5	10.0
Out-of-pocket cost ($M)	Traditional	2.8	5.0	15.0	40.0¶	–	150.0	40.0	252.8
	Chorus L2POC§	1.4	1.4	1.0	3.0	40.0¶	150.0	40.0	236.8
Capitalized cost ($M)*	Traditional	2.6	4.3	11.0	22.5	–	65.1	14.9	120.4
	Chorus L2POC	1.3	1.2	0.8	2.2	21.4	61.9	14.1	103.0
Probabilized capitalized cost ($M)‡	Traditional	2.6	3.9	7.6	7.6	–	6.4	1.0	29.1
	Chorus L2POC	1.3	1.1	0.6	0.7	3.9	6.1	1.0	14.7

CS, candidate selection; FED, first efficacy dose; FHD, first human dose; FL, first launch; FTD, first toxicology dose; FRD, first registration dose; FS, first submission; L2POC, lean-to-proof-of-concept; M, million; POC, proof of concept; *p*(TS), probability of technical success.*Cost of capital is 11%. Capitalized cost represents the present value of money and is calculated as the out-of-pocket cost divided by a discount factor that starts with a value of 1 for present time and grows by the cost of capital of 11% per year of development. The numbers in this table are based on a 0.5 year delay after POC in the Chorus L2POC model. A range of delays were evaluated in a sensitivity analysis as explained above. ‡The 'probabilized capitalized cost' is the capitalized cost adjusted by the probability that it would be incurred at each stage, which is a function of cumulative *p*(TS) up to the beginning of the stage. §Chorus L2POC out-of-pocket costs are the mean of all Chorus projects, both internally and externally funded (n = 46). ‖The financial model assumes 50% of the Phase II risk is removed at POC. ¶Post-POC Phase II development in the L2POC model is assumed to cost the same as the full Phase II programme in the traditional model. This is a simplistic approach that assumes that the cost of the additional activities needed to enable the rest of Phase II stage is offset by savings in the Phase II programme owing to the findings in the POC stage, which results in smaller more focused Phase IIb study designs.

drug development — among the various venture capitalists, biotech companies, specialty pharmaceutical companies and academic drug-development initiatives — operate at a sufficient scale to take advantage of this portfolio-based approach to improving overall R&D productivity. As Paul *et al.*[2] point out, pulling risk and attrition forward only makes sense when there is an abundance of actionable innovation at hand: that is, when the savings reaped from an early termination can be redirected to a more promising asset. Although Chorus shares the philosophy of 'not-pharma' with the biotech industry, the focus on portfolio efficiency is the key distinction between Chorus and the 'leanness' of the biotech industry. Owing to small portfolios and the need to show incremental value creation, small biotech organizations invest substantial resources, cycle time and opportunity costs in candidates even in the face of early signals of potential failure. Recently, investment funds with a larger portfolio of biotech, academically derived and repurposed pharma candidates have gained a similar strategic interest in L2POC portfolio management.

Application to early drug development. Although the 'candidate selection to POC' phase of drug development — with its high attrition and large value step up for positive data — is uniquely suited to the disruption aimed at improving pharmaceutical R&D productivity, the drug discovery (target to candidate selection) phase of drug development is also ripe for innovation. Recently, the cost and productivity of 'in-house' pharma discovery laboratories have been questioned[3]. The key steps of early drug development (that is, target identification, medicinal chemistry and non-clinical pharmacology) may be amenable to virtualized organizational approaches. Most crucially, this approach could harness the natural talent of academic groups (target discovery and non-clinical pharmacology) with the key skills of the pharmaceutical industry (medicinal chemistry, biopharmaceutics, efficient project management, commercial forecasting, etc.) as an initial solution to addressing the widely recognized 'valley of death' (REF. 27). Experience with Chorus suggests that this approach to the earlier phase of drug discovery would benefit from the key Chorus-like principles: lean development, efficient outsourcing, a small team of experienced drug discoverers and agnostic approaches to key project risks.

Future directions. Over the past decade, Chorus has developed a highly productive approach to early-phase pharmaceutical development. The founding principles have stood the test of time. Chorus is a learning organization and will continue to evolve. For Lilly, Chorus serves an additional function as a valuable 'test bed' for innovation in the drug development process. One attribute not yet mentioned is the empowerment of the staff engendered in this model. There is a very strong *esprit de corps* and 'act like an owner' mentality. No matter which of these new directions Chorus is asked to take, it is certain that the group will embrace the challenge and continue to find ways to do more work at higher quality for less.

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Competing interests statement
The authors declare no competing interests.