Lupus clinical development: will belimumab’s approval catalyse a new paradigm for SLE drug development?

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Introduction: Systemic lupus erythematosus (SLE) is a diverse autoimmune disease affecting many different organ systems. Although disease manifestations are varied across the lupus population, the widespread presence of autoantibodies indicates that SLE immunopathology involves B-cell dysregulation. Belimumab, a human anti-B-cell activating factor (BLyS) monoclonal antibody, was invented by Human Genome Sciences and co-developed with GlaxoSmithKline and became, in 2011, the first new therapy approved for SLE patients in over 50 years.

Areas covered: Belimumab approval represents a milestone as a new treatment for a subset of SLE patients and also a window onto the continued unmet need for many patients suffering from this diverse disease. This paper analyses the drugs and clinical trials of industry-sponsored development programs to profile the current SLE landscape and to consider how belimumab is shaping the future of SLE drug development.

Expert opinion: Our analysis demonstrates that the belimumab clinical program created a model for improvements in study designs that is reflected in ongoing clinical trials sponsored by a broad range of companies. Additional BLyS inhibitors, with distinctive targeting characteristics, are now in late stage development. A broad range of drugs with other mechanisms of action are also under investigation in Phase II–III trials, some of which are focused on the underserved lupus nephritis population.

Keywords: BAFF, belimumab, BLyS, clinical trial, lupus, pharmacotherapy, systemic lupus erythematosus

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1. Introduction

B-cell activating factor (BLyS), also commonly known as BAFF, emerged as a promising target for human systemic lupus erythematosus (SLE) drug development after investigational models identified it as a key survival factor for mature B cells [1,2]. Belimumab, a neutralising mAb that binds soluble BLyS, entered clinical development as a targeted lupus treatment only 2 years later [3]. The first SLE Phase II study enrolled adult SLE patients who had disease activity of SELENA-SLEDAI score ≥ 4 and a history of measurable autoantibodies, although seropositive status was not required at the time of screening [4]. Primary outcomes measured, for 3 doses of belimumab (plus standard of care [SOC]) versus SOC alone, were SELENA-SLEDAI score reduction at week 24 or reduction in time to first SLE flare over 52 weeks. The primary end points were not achieved in this study; however, exploratory subgroup analyses revealed that patients who were serologically positive at baseline experienced a significant improvement in SELENA-SLEDAI score at week 52 with belimumab [4]. Additional factors may have played a role in the trial
Industry sponsored clinical trials for SLE treatments encompass a broad range of drugs with a variety of mechanisms of action. Current clinical trial designs are strongly influenced by successes and shortcomings of the belimumab SLE clinical program. Treatment paradigm of drug development for RA also may succeed for SLE, with multiple molecular targets under development for the diverse lupus patient populations.

This box summarises key points contained in the article.

failing to achieve its primary outcomes, including an unexpectedly high early flare rate that made it difficult to detect any treatment effect and the allowance of unlimited use of co-medications throughout the 52 weeks of treatment that could have impacted the SLE disease activity assessments. Post hoc analysis of data from the more responsive, seropositive subjects was used to define a novel responder index, the Systemic Lupus Erythematosus Responder Index or SRI [5]. The SRI employed the SELENA-SLEDAI score to determine global improvement, British Isles Lupus Assessment Group (BILAG) domain scores to ensure no significant worsening in unaffected organ systems and the Physician’s Global Assessment (PGA) to evaluate overall condition. The two pivotal Phase III trials (BLISS-52 and BLISS-76) that followed were designed with refinements gleaned from the Phase II experience, including enrolling patients who were autoantibody positive and had active disease (SELENA-SLEDAI ≥ 6) at baseline and employed the SRI as the primary outcome measure. The BLISS-52 and BLISS-76 studies achieved significantly higher SRI rates in 52-week treatment regimens with belimumab plus SOC versus SOC alone [6]. However, the higher SRI improvement rates achieved at week 52 were modest in both studies, reaching 43.2 versus 33.5% (BLISS-76) and 57.6 versus 43.6% (BLISS-52) for belimumab-treated patients versus SOC only. The relatively modest efficacy observed in these trials could be due to the inherent challenges of treating a heterogeneous population with a specific targeted drug and from the limited incremental improvement above outcomes achieved by the aggressive SOC utilised in these studies. The meaningful clinical improvements achieved in these studies supported regulatory approval of belimumab for adult SLE patients with active, autoantibody-positive disease who are receiving standard therapy.

Prior to the 1998 approval of the first TNF-α antagonist, etanercept, rheumatoid arthritis (RA) treatment employed broad immunosuppressants and steroids, similar to the SOC treatment for SLE, that were often inadequate for the majority of this patient population. With belimumab’s validation of the BLYs pathway in human lupus, could SLE clinical development now mirror the clinical development paradigm previously observed for RA, in which TNF antagonists formed the basis for the first targeted biologics? Is the belimumab clinical program the catalyst that will spur additional BLYs targeting clinical programs, as well as programs that target other molecular pathways in lupus, much as TNF antagonists did for RA programs?

2. Competitive landscape for drugs in planned or ongoing industry-sponsored SLE clinical trials

This summary bull’s eye chart (Figure 1) provides a snapshot of drugs in Phase II and III lupus trials and highlights their therapeutic classes or mechanisms of action (MOAs). The chart also highlights the specific patient population enrolled in these trials, including lupus nephritis and cutaneous lupus, illustrating how sponsors are targeting certain subsets of the diverse lupus population. The scope of this analysis is confined to planned or ongoing trials of drugs that have completed Phase I trials, because Phase I studies generally focus on preliminary safety outcomes and have limited efficacy outcomes for analysis.

2.1 Summary of drugs, sponsors and phases for current industry-sponsored trials

Drugs in Phase II development (24) are diverse and include many biologics, a broad range of immunosuppressants and protein kinase inhibitors. Ongoing Phase III trials evaluate the novel BLYs inhibitors tabalumab and blisibimod, and the expanded usage or safety of belimumab (Benlysta). Belimumab has not completed trials in severe active lupus nephritis or severe active central nervous system lupus patients for whom the SOC remains the best treatment option currently. Therefore, continued clinical development is required to address the unmet need in these patient populations.

Drugs in Phase III trials (9) also include some that are approved for other diseases: abatacept and mycophenolic acid (both in trials for lupus nephritis) and salbutamol. In addition, the approved SLE drug, hydroxychloroquine (Plaquenil), is being evaluated in a single Japanese cutaneous lupus study by Sanofi [7]. These drugs have established safety profiles that could expedite their development if they prove effective in lupus nephritis and cutaneous lupus. In addition, new compounds blisibimod, epratuzumab, forigerimod and tabalumab are advancing in Phase III SLE development.

Table 1 contains more detailed drug information and provides the sponsor, current clinical phase and molecular target details. The industry sponsors are nearly as numerous as the drugs. The top sponsors have a narrow focus and include AstraZeneca (IFN [type 1] antagonists), UCB (epratuzumab), Anthera (blisibimod) and Eli Lilly (tabalumab). There are 18 biologics under development that comprise 13 mAbs, 3 fusion proteins (abatacept, SM101, atacicept), a peptibody (blisibimod) and a vaccine (IFN-α/kinoid).

Two pipeline BLYs inhibitors (tabalumab, blisibimod), with distinctive targeting characteristics, are in trials and have the
potential to exhibit different therapeutic profiles from that of belimumab. The BLyS ligand exists in two soluble forms (homotrimers and 60-mer capsids) and a membrane-bound form, which bind to three different receptors, BCMA, TACI and BAFF-R [8]. Whereas belimumab binds exclusively to the soluble form of BLyS [9], tabalumab, a humanised mAb binds both soluble and membrane-bound forms of BlyS [10] and could more broadly block the pathway. Blisibimod is a peptibody, a Fc conjugated to a peptide, that binds to BLyS. Antagonists of the IFN (type 1) pathway are of keen interest, as illustrated by the development of five pipeline therapeutics with this MOA. AstraZeneca, Roche, Neovacs and Resolve Therapeutics (in partnership with Takeda) are developing biologic therapies targeting either type 1 IFN ligands or the receptor chain, IFNAR1. New biologics are aimed at blockade of the CD22, TWEAK, CD74, CD32, CCR5 and IFN-γ pathways. Several anti-inflammatory targets under evaluation for SLE are already proven to be important pathways from RA therapeutics. These include two anti-IL-6 mAbs (Pfizer’s PF-4236921 and Johnson & Johnson’s sirukumab) and three pipeline protein kinase inhibitors (GSK-2586184, R-333 and PRT-062607). The immunosuppressant class of drugs encompasses many molecular targets. The pipeline drugs (laquinimod and forigerimod) in development programs sponsored by Teva and ImmulPharma, respectively, are novel and are poised to enter Phase III.

2.2 MOAs for drugs in current SLE trials

Although a wide variety of MOAs are in planned or ongoing trials, certain molecular targets stand out in the trial counts (Figure 2). The BLyS inhibitors are clearly the most numerous with 14 trials, followed by the IFN (type 1) antagonists. Other molecular targets with more than one trial include CD22 (epratuzumab), TWEAK (BIIB-023) and IL-6 (PF-4236921, sirukumab).

3. Study design and primary outcome analysis for current SLE clinical trials

The current intensification in SLE clinical development may be spurred by belimumab’s successful Phase III clinical program, which benefited from careful exploratory and post hoc analyses of responder groups of the Phase II study to improve
study design. The novel composite SRI derived from those analyses was employed as the primary end point in belimumab pivotal trials [11].

### 3.1 Study design analysis of primary outcomes for current SLE clinical trials

To determine how broadly the SRI is being utilised in current trials, primary end points of 41 trials, for which this information was available, were assessed (Figure 3). SLE studies evaluating this composite end point included five Phase II and eight Phase III trials. In addition, safety remains an important end point for most SLE trials and is the most common the primary outcome disclosed for Phase II trials (12 of 22 Phase II studies). As expected, safety is less frequently a primary outcome in Phase III trials (4 of 19). Clearly, the novel SRI end point has been widely adopted as a primary outcome to evaluate efficacy in SLE trials. Another novel composite end point, the BICLA, was derived in an earlier epratuzumab
study [12] and is being employed in three ongoing Phase III studies, with two of these studies utilising it as the primary outcome. The BICLA composite index includes BILAG-2004, SLEDAI-2K, PGA of disease activity and a 'no treatment failure' criterion [12]. For trials evaluating outcomes for lupus nephritis (renal response outcomes) and cutaneous lupus percent responders [cutaneous], other end points are evaluated.

3.2 Biomarker analysis in current SLE trials

The diversity of SLE disease symptoms suggest that selecting potentially responsive patients, by biomarkers or pharmacogenomic (PGX) markers, could improve the prospects of delivering effective treatment to a selected patient population. Two epratuzumab Phase III trials, and the Phase II GSK-2586184 trial, have disclosed evaluation of biomarkers and/or PGX marker. Roche has developed a quantitative polymerase chain reaction assay that profiles IFN-regulated genes [13] as a companion diagnostic for their rontalizumab program, which could hone the focus of development for this drug by identifying SLE patients with specific IFN signature profiles to correlate with clinical responses.

4. Summary of success or failure of drugs with MOAs

Although past success (or failure) may not be a perfect predictor of future outcomes, it is informative to consider the trial outcomes reported for primary outcomes assessed in trials for some of the MOAs under current clinical investigation. A total of 16 completed or terminated Phase II and Phase III trials for four MOAs in current SLE development had trial outcomes available for evaluation (Figure 4).

4.1 Primary outcomes for ongoing trials evaluating B-cell targeting drugs

BLyS inhibitors, atacicept and blisibimod, returned negative outcomes, each in a single trial [14,15]. In addition, a Phase II/III atacicept trial in lupus nephritis patients was terminated due to safety/adverse events (increased risk of serious infections) [16]. Further development of these drugs continues. Merck KGaA/EMD Serono had no planned or ongoing clinical studies for atacicept at the time of our data analysis. However, a Phase IIIb atacicept (subcutaneous) study was initiated in November
2013 for the treatment of moderately active SLE [17] which is evaluating the SRI at week 24 as the primary outcome.

Positive primary end point outcomes have been reported for the CD22 antagonist, epratuzumab. Although three epratuzumab trials (ALLEVIATE 1 and 2 Phase III trials and their extension study) were terminated due to interruption of drug supply, these trials reported no efficacy or safety concerns [12]. Two anti-CD20 therapies have been discontinued for lupus development following the negative outcomes. Two rituximab Phase III trials, the EXPLORER study [18] that enrolled SLE patients with moderate-to-severe disease and the LUNAR study [19] that enrolled patients with lupus nephritis, returned negative outcomes. An ocrelizumab Phase III trial performed in patients with active lupus nephritis was termination due to safety/adverse events [20]. The negative outcomes of the CD20 antagonists (ocrelizumab, rituximab) illustrate some of the challenges of inhibiting broader B-cell pathways. Indeed, Immunomedics announced in October 2013, after our original data analysis, that Takeda terminated their license agreement to develop the humanised anti-CD20 mAb, veltuzumab, for all non-cancer indications. It will be intriguing to see how current BlyS inhibitors and epratuzumab strike the therapeutic balance required to suppress autoimmunity, while preserving normal immune responses.

### 4.2 Primary outcomes for ongoing trials evaluating IFN (type 1) antagonists

Early studies reported positive outcomes for IFN (type 1) antagonists (sifalimumab, IFN-α kinase and rontalizumab). The primary outcomes reported as positive for IFN (type 1) antagonists are currently only from Phase II studies. The IFN-α kinase and sifalimumab Phase II studies reported primary outcomes of safety and tolerability only [21,22]. The rontalizumab Phase II study enrolled patients with moderate-to-severe, active SLE and reported that treatment (in the absence of immunosuppressants) was associated with improvement in signs and symptoms of SLE [23]. The positive outcomes (increased SRI response rates and reduced SELena-SLEDAI flare rates) for rontalizumab treatment (vs placebo) were described for a biomarker-defined, pre-specified subgroup of subjects [23]. Time will tell how these therapeutic agents will perform in larger, more robust Phase III trials.

### 5. Projected timelines for the SLE drug candidates in current Phase II - III studies

One of the hopeful signs of promising new lupus therapies is that the multitude of pharmaceutical companies are currently committed to developing safer and more effective drugs for this debilitating disease. Phase II and III clinical trial activity in lupus is promising with 50 trials being run for the foreseeable future and encompassing 34 drugs and 27 sponsors (Table 2). The table provides the primary end points and predicted timeframe for primary end point results and shows that six of the therapies in Phase III could be reporting data in 2014. Additionally, eight Phase II trials are expected to have results by the end of 2013, whereas nine others will report during 2014.
Table 2. Forecasted completion dates of planned and ongoing industry-sponsored Phase II – III programs in lupus.

| Primary drug | Sponsorship | Trial Phase | Trial status | Primary end points | Start date | Primary end points forecast |
|--------------|-------------|-------------|--------------|--------------------|------------|----------------------------|
| Belimumab (i.v.) | GSK | III | Closed | Safety | 8/1/2008 | 5/1/2015 |
| | | III | Open | SRI | 5/31/2011 | 7/26/2014 |
| | | III | Open | Safety | 6/1/2012 | 6/26/2018 |
| | | III | Open | Renal response outcomes | 7/1/2012 | 2/1/2017 |
| | | II | Closed | Safety | 5/1/2005 | 5/1/2016 |
| | | II | Open | SRI (paediatric) | 9/1/2012 | 3/1/2016 |
| Belimumab (s.c.) | UCB | III | Open | SRI | 11/1/2011 | 11/1/2014 |
| Epratuzumab | UCB | III | Open | BICLA | 12/14/2010 | 11/1/2014 |
| | | III | Open | BICLA | 12/14/2010 | 11/1/2014 |
| | | III | Open | Safety | 7/1/2011 | 12/2/2015 |
| Blisibimod | Anthera | III | Open | Safety | 1/1/2012 | 11/2/2014 |
| | | III | Planned | SRI-8 | 2/1/2013 | 2/13/2016 |
| | | III | Planned | Renal response outcomes | 2/15/2014 | 2/15/2017 |
| Tabalumab | Eli Lilly | III | Closed | Safety | 3/1/2014 | 2/26/2017 |
| R-salbutamol | Astion | III | Open | Percent responders [cutaneous] | 11/7/2007 | 3/21/2010 |
| Hydroxychloroquine | Sanofi | III | Closed | Percent responders [cutaneous] | 3/1/2012 | 1/1/2014 |
| Mycophenolic acid | Novartis | III | Open | Renal response outcomes | 7/1/2012 | 6/28/2016 |
| | | III | Planned | Renal response outcomes | 2/1/2013 | 7/1/2017 |
| Abatacept | BMS | III | Open | Safety | 2/15/2014 | 2/14/2016 |
| | | III | Planned | Not available | 4/1/2014 | 4/17/2016 |
| Sifalimumab | AstraZeneca | III | Planned | Not available | 4/1/2014 | 4/17/2016 |
| Forgerimod | ImmuPharma | III | Planned | Not available | 2/15/2014 | 2/14/2016 |
| | | III | Planned | Renal response outcomes | 2/1/2013 | 7/1/2017 |
| Sifalimumab (i.v.) | AstraZeneca | II | Closed | Safety | 8/1/2010 | 11/1/2013 |
| | | II | Closed | SRI | 4/26/2011 | 2/17/2013 |
| Sifalimumab (i.v.), sifalimumab (s.c.) | AstraZeneca | II | Open | Safety | 11/1/2009 | 9/1/2013 |
| Anifrolumab | AstraZeneca | II | Open | SRI | 1/24/2012 | 3/1/2014 |
| | | II | Open | Safety | 4/20/2012 | 4/1/2017 |
| | | II | Open | Safety | 3/1/2013 | 4/1/2014 |
| | | II | Planned | Renal response outcomes | 7/1/2012 | 9/1/2016 |
| BIIIB-023 | Biogen Idec | II | Planned | Safety | 11/1/2013 | 11/1/2018 |
| | | II | Planned | Renal response | 8/1/2011 | 9/1/2013 |
| Sirukumab | Johnson & Johnson | II | Closed† | | 2/23/2012 | 3/1/2013 |
| | | II | Open | Reduction of the disease activity | 7/11/2011 | 7/1/2013 |
| | | II | Open | Percent responders [cutaneous] | 8/1/2011 | 10/1/2014 |
| | | II | Open | Percent responders | 8/1/2011 | 10/1/2014 |
| | | II | Open | Renal response outcomes | 2/23/2012 | 3/1/2013 |
| | | II | Open | Erythema and scaling score | 9/1/2012 | 9/1/2013 |
| | | II | Open | Safety, Biomarkers, SELENA SLEDAI score | 3/1/2013 | 11/1/2014 |
| | | II | Planned | Safety | 7/1/2013 | 1/1/2015 |
| | | II | Planned | Safety, Biomarker | 7/18/2013 | 7/1/2014 |
| | | II | Planned | Not available | 4/1/2013 | 10/1/2014 |
| | | II | Planned | Not available | 10/1/2013 | 3/16/2015 |

*Atacicept trial initiated after 23 September 2013.
†Recently completed.
i.v.: Intravenous; s.c.: Subcutaneous; SRI-8: Systemic Lupus Erythematosus Response Index-8.
Table 2. Forecasted completion dates of planned and ongoing industry-sponsored Phase II – III programs in lupus (continued).

| Primary drug | Sponsorship | Trial Phase | Trial status | Primary end points | Start date | Primary end points forecast |
|--------------|-------------|-------------|--------------|--------------------|------------|-----------------------------|
| PRT-062607   | Biogen Idec, Portola | II          | Planned      | Not available      | 2/15/2014  | 5/10/2015                   |
| Voclosporin   | Isotechnika, Vifor   | II          | Planned      | Not available      | 2/15/2014  | 5/10/2015                   |
| Clarithromycin + clofazimine + rifabutin | RedHill | II          | Planned      | Not available      | 4/1/2014   | 6/24/2015                   |
| RSVL-132     | Resolve        | III         | Planned      | Safety             | 2/15/2014  | 7/15/2014                   |
| milatuzumab   | Immunomedics    | III         | Planned      | Safety, BILAG      | 1/1/2014   | 1/30/2016                   |

*Atacicept trial initiated after 23 September 2013.
*Recently completed.

i.v.: Intravenous; s.c.: Subcutaneous; SRI-8: Systemic Lupus Erythematosus Response Index-8.

6. Conclusion

The belimumab clinical program achieved the first approval for a targeted SLE treatment, while creating a model for improving study design that is reflected in ongoing clinical trials today. Belimumab’s launch also encouraged further BLyS inhibitor development and includes drugs with distinctive targeting characteristics that could provide additional therapeutic value. Phase III SLE programs are slated to return results in 2014 for both BLyS inhibitors and alternative B-cell pathways, whereas trial readouts for other immunological regulators, such as IFN (type I) and cytotoxic T-lymphocyte antigen 4 pathway antagonism, lie in the more distant future. Clinical trial activity is also focused on expanding therapeutics into the underserved lupus nephritis subpopulation and on utilising biomarkers to define potentially responsive SLE patients to improve study outcomes.

7. Expert opinion

Belimumab’s impact on SLE therapeutics extends beyond the success of its approval for seropositive, adult SLE patients and the validation of the BLyS pathway for lupus therapeutics. The focus on honing clinical trial design changed the way SLE trials are run today. The adoption of the SRI index, observed for ongoing clinical trials, has inspired additional refinements for trials being run in this diverse disease population. Another novel responder index, the BICLA, was developed as part of the epratuzumab Phase II studies and is being employed for the program’s ongoing Phase III trials.

Additional inhibitors of BLyS are in late stage clinical trials and exhibit distinctive targeting characteristics that could translate into different therapeutic profiles. Tabalumab is a humanised mAb that neutralises both soluble and membrane-bound BLyS. It entered lupus clinical studies at Phase III with an acceptable safety profile from repeat-dosing RA studies [10]. The TACI-Ig fusion protein, atacicept, has returned to clinical trials very recently, as well [16]. This BLyS receptor fusion protein can bind to BLyS and to another TNF-family ligand, APRIL, a factor that plays an important role in survival of long-living plasma cells [24] and may be implicated in autoimmune diseases [25]. Both tabalumab and atacicept, thus, have the potential to more fully block the BLyS signalling pathway and could lead to improved efficacy or potentially result in new safety signals, not observed with belimumab treatment. The projected timelines of mid-2014 for the key tabalumab Phase III efficacy results, together with its good safety record to date, place it first in line for approval in B-cell-dependent lupus patients. Both atacicept and blisibimod have returned some negative clinical results, suggesting slower clinical progress and potential challenges to their approval.

The RA paradigm of drug development included follow-on TNF antagonists [26]. However, biologics targeting other molecular pathways were successfully developed for RA treatment later and included B7 antagonists (abatacept), IL-6 antagonists (tocilizumab) and Janus kinase (JAK) inhibitors (tofacitinib). Similar approaches are now being taken in SLE clinical programs. Clinical outcomes for an abatacept trial in the broader SLE population were not positive in a Phase II study that enrolled moderate-to-severe SLE [27]. The drug is now being evaluated further in another lupus nephritis study projected to complete in mid-2017 [28]. In addition, pipeline IL-6 antagonists and JAK inhibitors are in Phase II development, currently with similar longer-term timelines to achieve their primary end points.

Alternative B-cell targeting pathways have ongoing clinical trials. Notably, the CD22 antagonist, epratuzumab, is in late stage SLE development. Earlier epratuzumab SLE trial results were largely positive and there have been no major safety signals disclosed to date [29]. The epratuzumab studies include biomarker analyses and utilise a novel responder index, BICLA, which together could position this program well for regulatory success. This biologic could prove its merits by the end of 2014. In contrast, CD20 antagonism has not proven safe or effective in earlier trials for ocrelizumab or rituximab, and future development would likely require study...
design improvements [30]. Despite the failure of rituximab trials, investigators have used rituximab off label with some success in treating refractory lupus patients [31,32]. The only anti-CD20 in development recently, veltuzumab, has been discontinued by Teva, possibly due to the challenges in developing a CD20 antagonist for SLE.

A role for type 1 interferons in the pathogenesis of SLE is well supported [33]. Clinical trials for IFN (type 1) antagonists have demonstrated safety in phase studies to date, but their efficacy remains to be demonstrated in robust Phase III trials. These trials are projected to start in 2014 and could include mAbs targeting either IFN (type 1) ligands or the shared type 1 IFN receptor, IFNAR1. The IFNs (type 1) are a large family of proteins that bind to and signal through a single receptor complex. Therefore, blockade of the receptor by AstraZeneca’s anifrolumab might have a greater impact on the pathway than the ligand-binding mAbs, sifalimumab and rontalizumab. AstraZeneca’s anti-IFN-α mAb, sifalimumab, may be the first of these to enter Phase III. However, Roche’s rontalizumab, which returned positive primary outcome results in 2012 [23], may be poised to enter Phase III with a companion diagnostic that could define a responsive patient population through their IFN signature. Development programs that narrow the focus to a specific patient population by means of a biomarker, and also hone the study design, will be best positioned to discern therapeutic advantages for treatment in this diverse disease population.

Direct antagonists of the IFN (type 1) pathway have reached Phase II studies already. Toll-like receptors (TLR), mediators of innate immunity which lead to upregulation of IFN (type 1) genes, have also emerged as attractive therapeutic targets [34]. The clinical development for antagonists of these pathways is still at a very early stage. The most advanced TLR antagonist (IMO-8400, Idera’s TLR 7, 8, 9 antagonists) is poised to enter Phase II. In addition, blockade of the proinflammatory, IFN (type 2) and IFN-γ is another approach in active development. Anti-IFN-γ mAbs are in Phase I studies currently and include Amgen’s AMG 511 and NovImmune’s NI-0501 [35-37].

Antagonising immune system function is a balancing act. However, the broad range of MOAs under investigation in SLE, plus the intensification of trial activity by multiple industry sponsors, points towards development that could lead to a spectrum of SLE therapies that mirror the therapeutic successes seen for RA.

**Declaration of interest**

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