

Antibodies to watch in 2017

Janice M. Reichert

Executive Director, The Antibody Society, Framingham, MA, USA

ABSTRACT

Over 50 investigational monoclonal antibody (mAb) therapeutics are currently undergoing evaluation in late-stage clinical studies, which is expected to drive a trend toward first marketing approvals of at least 6–9 mAbs per year in the near-term. In the United States (US), a total of 6 and 9 mAbs were granted first approvals during 2014 and 2015, respectively; all these products are also approved in the European Union (EU). As of December 1, 2016, 6 mAbs (atezolizumab, olaratumab, reslizumab, ixekizumab, bezlotoxumab, oblitoxaximab) had been granted first approvals during 2016 in either the EU or US. Brodalumab, was granted a first approval in Japan in July 2016. Regulatory actions on marketing applications for brodalumab in the EU and US are not expected until 2017. In 2017, first EU or US approvals may also be granted for at least nine mAbs (ocrelizumab, avelumab, Xilonix, inotuzumab ozogamicin, dupilumab, sirukumab, sarilumab, guselkumab, romosozumab) that are not yet approved in any country. Based on announcements of company plans for regulatory submissions and the estimated completion dates for late-stage clinical studies, and assuming the study results are positive, marketing applications for at least 6 antibody therapeutics (benralizumab, tildrakizumab, emicizumab, galcanezumab, ibalizumab, PRO-140) that are now being evaluated in late-stage clinical studies may be submitted during December 2016* or 2017. Other ‘antibodies to watch’ in 2017 include 20 mAbs are undergoing evaluation in pivotal studies that have estimated primary completion dates in late 2016 or during 2017. Of these, 5 mAbs are for cancer (durvalumab, JNJ-56022473, ublituximab, anetumab ravtansine, glembatumumab vedotin) and 15 mAbs are for non-cancer indications (caplacizumab, lanadelumab, roledumab, tralokinumab, risankizumab, SA237, emapalumab, suptavumab, erenumab, eptinezumab, fremanezumab, fasinumab, tanezumab, lampalizumab, brolocizumab). Positive results from these studies may enable submission of marketing applications in 2017 or 2018, or provide justification for additional studies. *See note added in proof for update through December 31, 2016.

Abbreviations: ADC, antibody-drug conjugate; AML, acute myeloid leukemia; BLA, biologics license application; EMA, European Medicines Agency; FDA, US Food and Drug Administration; HNSCC, head and neck squamous cell carcinoma; IV, intravenous; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; PK, pharmacokinetics; PASI, Psoriasis Area and Severity Index; RA, rheumatoid arthritis; SC, subcutaneous

ARTICLE HISTORY

Received 5 December 2016
Accepted 5 December 2016

KEYWORDS

Antibody therapeutics; cancer; European Medicines Agency; Food and Drug Administration; immune-mediated disorders

Introduction

Since 2010, the ‘Antibodies to watch’ article series^{1–9} has documented key events in the commercial development of monoclonal antibody (mAb) therapeutics, with a focus on initiation of first pivotal clinical studies, submission of the first marketing applications to the European Medicines Agency (EMA) or the US Food and Drug Administration (FDA), and first marketing approvals. This report on ‘Antibodies to watch in 2017’ includes details of 52 mAbs currently in late-stage studies for cancer (20 mAbs) or non-cancer (32 mAbs) indications, 9 mAbs with first marketing applications under review, and 7 antibodies that were granted first marketing approvals in 2016. Due to the substantial amount of literature on these antibody therapeutics, only recent clinical study results are cited.

First approvals granted during 2016

As of December 1, 2016, 7 monoclonal antibody (mAb) therapeutics had been granted their first marketing approvals in 2016. Of

these, 6 were granted first approvals in either the European Union (EU) or United States (US) (Table 1), and 1 (brodalumab) was granted its first approval in Japan. The approvals included 2 mAbs for cancer (atezolizumab, olaratumab), 3 mAbs for immune-mediated disorders (reslizumab, ixekizumab, brodalumab) and 2 mAbs for infectious diseases (bezlotoxumab, oblitoxaximab).

Atezolizumab (Tecentriq®) was approved in the US for treatment of patients with locally advanced or metastatic urothelial carcinoma in March 2016. The mAb received breakthrough therapy designation, priority review status and accelerated approval for this indication. Atezolizumab, which targets programmed cell death ligand 1 (PD-L1), was subsequently approved by the FDA for non-small cell lung cancer in October 2016. As of November 2016, atezolizumab was not approved in the EU, but a marketing authorization application was undergoing evaluation by the EMA. The mAb’s target, PD-L1, interacts with programmed death receptor 1 (PD-1), which negatively regulates T-cell receptor signaling and inhibits

CONTACT Janice M. Reichert ✉ janice.reichert@antibodysociety.org Editor-in-Chief, *mAbs*, Executive Director, The Antibody Society, 247 Prospect Street, Framingham, MA 01701, USA.

Published with license by Taylor & Francis Group, LLC © Janice M. Reichert

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited, and is not altered, transformed, or built upon in any way.

Table 1. Therapeutic monoclonal antibodies first approved in the European Union or the United States during 2016.*

International non-proprietary name	Brand name	Target; Format	Indication first approved	First EU approval year	First US approval year
Atezolizumab	Tencentriq	PD-L1; Humanized IgG1	Bladder cancer	In review	2016
Olaratumab	Lartruvo	PDGFR α ; Human IgG1	Soft tissue sarcoma	2016	2016
Reslizumab	Cinqaero, Cinqair	IL-5; Humanized IgG4	Asthma	2016	2016
Ixekizumab	Taltz	IL-17a; Humanized IgG4	Psoriasis	2016	2016
Bezlotoxumab	Zinplava	<i>Clostridium difficile</i> enterotoxin B; Human IgG1	Prevention of <i>Clostridium difficile</i> infection recurrence	In review	2016
Obiltoximab	Anthim	Protective antigen of <i>B. anthracis</i> exotoxin; Chimeric IgG1	Prevention of inhalational anthrax	NA	2016

*Data as of December 1, 2016; a comprehensive table of approved antibody therapeutics and those in regulatory review in the EU or US is maintained on The Antibody Society's website (www.antibodysociety.org).

Abbreviations: CD, cluster of differentiation; EC, European Commission; IL, interleukin; NA, not approved or in review in the EU; PDGFR, platelet-derived growth factor receptor; PD-L1, programmed death ligand 1.

anti-tumor T-cell function. While atezolizumab is the first anti-PD-L1 antibody to be approved, two anti-PD-1 antibodies, nivolumab and pembrolizumab were granted approvals in 2014. Nivolumab is approved for Hodgkin lymphoma, metastatic melanoma, metastatic renal cell carcinoma, and squamous non-small cell lung cancer and recurrent or metastatic squamous cell carcinoma of the head and neck; pembrolizumab is approved for non-small cell lung cancer, metastatic melanoma, and recurrent head and neck squamous cell carcinoma (HNSCC). Atezolizumab is currently undergoing evaluation in Phase 3 studies of patients with other types of cancer, including breast cancer, renal cell carcinoma, bladder cancer, and small-cell lung cancer.

Olaratumab (Lartruvo[®]), a human IgG1 that targets platelet-derived growth factor receptor α (PDGFR α) was granted a first approved by FDA in October 2016 for soft tissue sarcoma. The mAb received Fast Track, breakthrough therapy and orphan drug designations, priority review status and accelerated approval in the US for this indication. In November 2016, the European Commission granted a conditional marketing authorization for olaratumab in combination with doxorubicin for the treatment of adult patients with advanced soft tissue sarcoma who are not amenable to curative treatment with surgery or radiotherapy and who have not been previously treated with doxorubicin. In the EU, a conditional marketing authorization can be granted to a medicinal product that fulfils an unmet medical need when the benefit to public health of immediate availability outweighs the risk inherent in the fact that additional data are still required. Olaratumab has an EU orphan drug designation for soft tissue sarcoma. The safety and efficacy of olaratumab was evaluated in an open-label, randomized, active-controlled study of 133 patients with soft tissue sarcoma. The median overall survival and progression-free survival for patients who received olaratumab with doxorubicin were 26.5 and 8.2 months, respectively, compared with 14.7 and 4.4 months, respectively, for patients taking doxorubicin only.¹⁰ Results from the ongoing Phase 3 ANNOUNCE study (NCT02451943) comparing the olaratumab/doxorubicin combination with doxorubicin alone in patients with advanced or metastatic soft tissue sarcoma may be used to support a continued authorization.

Reslizumab (Cinqair[®], Cinqaero[®]), an anti-interleukin (IL)-5 humanized mAb produced in mouse myeloma cells (NS0), was granted marketing approvals by FDA and the European

Commission in March and August 2016, respectively. In the US, the product is indicated for add-on maintenance treatment of patients with severe asthma aged 18 y and older, and with an eosinophilic phenotype. In the EU, reslizumab is indicated as add-on therapy in adult patients with severe eosinophilic asthma inadequately controlled despite high-dose inhaled corticosteroids plus another medicinal product for maintenance treatment. The recommended dose is 3 mg/kg once every four weeks given by intravenous (IV) infusion over 20–50 minutes.

Ixekizumab (Taltz[®]), an anti-IL-17A humanized mAb produced in Chinese hamster ovary (CHO) cells, was granted marketing approvals by FDA and the European Commission in March and May 2016, respectively. In the US and EU, ixekizumab is indicated for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy; the prescribing information in the US indicates that adults with moderate-to-severe plaque psoriasis who are candidates for phototherapy may also receive the product. The recommended dose is 160 mg by subcutaneous (SC) injection (two 80 mg injections) at Week 0, followed by 80 mg (one injection) at Weeks 2, 4, 6, 8, 10, and 12, then maintenance dosing of 80 mg (one injection) every 4 weeks.

Brodalumab (LUMICEF[®]) is a human anti-IL-17 receptor A mAb that inhibits biological activity of IL-17A, IL-17F and other IL-17s. The product was granted a first marketing approval from the Ministry of Health, Labor and Welfare in Japan on July 4, 2016 for the treatment of psoriasis vulgaris, psoriatic arthritis, pustular psoriasis, and psoriatic erythroderma. In adults, the recommended dose is 210 mg SC administered at Weeks 0, 1, and 2, followed by 210 mg every 2 weeks. A biologics license application (BLA) for brodalumab is undergoing review by FDA. In July 2016, the FDA's Dermatologic and Ophthalmic Drugs Advisory Committee voted 18 to 0 to recommend approval of brodalumab injection, 210 mg, for adult patients with moderate-to-severe plaque psoriasis. FDA's action date for the application, November 16, 2017, was delayed by 3 months, and the action date is now February 16, 2017. A marketing authorization application for brodalumab in psoriasis is undergoing evaluation by EMA.

Bezlotoxumab (ZINPLAVATM), a human IgG1 mAb targeting *Clostridium difficile* toxin B, was granted an approved by FDA in October 2016 for reduction of *Clostridium difficile* infection (CDI) recurrence in adults who are receiving antibacterial drug treatment of CDI and are at a high risk for CDI

recurrence. The recommended dose is a single dose of 10 mg/kg administered as an IV infusion over 60 minutes. A marketing authorization application for bezlotoxumab is undergoing evaluation by EMA.

Oblitoximab (ANTHIM[®]) is a chimeric IgG1 targeting the protective antigen of *Bacillus anthracis* exotoxin. The product was approved by FDA in March 2016. Oblitoximab is indicated in adult and pediatric patients for treatment of inhalational anthrax due to *Bacillus anthracis* in combination with appropriate antibacterial drugs, and for prophylaxis of inhalational anthrax when alternative therapies are not available or appropriate. A dose-dependent increase in survival after treatment with oblitoximab was observed in New Zealand White rabbits and cynomolgus macaques challenged with spores of the Ames strain of *Bacillus anthracis* administered by inhalation. The recommended dosage for adult patients is 16 mg/kg; for pediatric patients, the recommended dose ranges from 16–32 mg/kg depending on the weight of the patient. The safety and pharmacokinetics (PK) of the product were studied in adult healthy volunteers; no studies included patients with inhalation anthrax. There were no studies of safety or PK of oblitoximab in the pediatric population; a population PK approach was used to predict a dose that would provide pediatric patients with exposure comparable to the observed exposure in adults.

Regulatory actions: Projections for 2017

As of December 1, 2016, marketing applications for ten antibody therapeutics (Table 2) are being evaluated by either FDA or EMA for possible first approvals in the US or EU, respectively. Of these 10 mAbs, nine (ocrelizumab, avelumab, Xilonix, inotuzumab ozogamicin, dupilumab, sirukumab, sarilumab, guselkumab, romosozumab) are not yet approved in any country.

Ocrelizumab (OCREVUS) is a humanized IgG1 mAb targeting CD20. Marketing applications for ocrelizumab for the treatment of relapsing multiple sclerosis and primary progressive multiple sclerosis (MS) are being reviewed by EMA and FDA. Ocrelizumab was granted FDA's Breakthrough Therapy designation, and its application received priority review. FDA's action date for the application is March 28, 2017. The

marketing applications are based on positive results from three Phase 3 studies, OPERA I (NCT01247324), OPERA II (NCT01412333), and ORATORIO (NCT01194570). Identical in their study design, OPERA I and OPERA II evaluated the efficacy and safety of 600 mg ocrelizumab IV administered every six months compared with 44 µg interferon β-1a (Rebif[®]) SC administered 3 times per week in 1,656 people with relapsing forms of MS. Compared with Rebif[®], ocrelizumab showed superior efficacy in reducing annualized relapse rates and disability progression sustained for at least three and for at least six months.¹¹ The ORATORIO study evaluated the efficacy and safety of 600 mg ocrelizumab administered by IV infusion every six months compared with placebo in 732 people with primary progressive MS. Compared to patients who received placebo, patients who received ocrelizumab in this study showed significant reductions in disability progression sustained for at least three and for at least six months, as well as in other measures of progressive disease.¹¹

Avelumab, an anti-PD-L1 human IgG1 mAb, is undergoing review by EMA and FDA as a treatment for metastatic Merkel cell carcinoma. The marketing applications are based on data from the Phase 2 JAVELIN Merkel 200 study (NCT02155647), which demonstrated meaningful tumor responses in patients with metastatic disease that progressed after prior chemotherapy.¹² Avelumab received an orphan drug designation from EMA. Avelumab was granted Breakthrough Therapy, Fast Track and orphan drug designations by FDA for Merkel cell carcinoma; the BLA was granted a priority review. Avelumab is also undergoing evaluation in Phase 3 studies of patients with other types of cancers, including non-small cell lung, renal cell, ovarian, gastric and urothelial cancers.

XilonixTM is a human mAb targeting IL-1α undergoing review by EMA as a treatment for metastatic colorectal cancer. An opinion by CHMP on the marketing authorization application for XilonixTM is anticipated in 2016; if the opinion is favorable, a decision by the EC would likely occur in 2017. The application includes data from a Phase 3 study that showed a 76% relative improvement in response rate in patients treated with XilonixTM compared with placebo (33% vs. 19%, respectively; *p* = 0.0045).¹³ XilonixTM was granted Fast Track designation for cancer anorexia-cachexia syndrome by FDA.

Table 2. Therapeutic monoclonal antibodies in review* in the European Union or the United States.

International non-proprietary name	Proposed brand name	Target; Format	Indication	Status in EU	Status in US
Ocrelizumab	OCREVUS	CD20; Humanized IgG1	Multiple sclerosis	In review	In review
Avelumab	(Pending)	PD-L1; Human IgG1	Merkel cell carcinoma	In review	In review
(Pending)	Xilonix	IL-1 α; Human IgG1	Advanced colorectal cancer	In review	NA
Inotuzumab ozogamicin	(Pending)	CD22; Humanized IgG4; ADC	Hematological malignancy	In review	NA
Dupilumab	Dupixent	IL-4R α; Human IgG4	Atopic dermatitis	In review	In review
Sirukumab	(Pending)	IL-6; Human IgG1	Rheumatoid arthritis	In review	In review
Sarilumab	(Pending)	IL-6R; Human IgG1	Rheumatoid arthritis	In review	In review
Brodalumab#	LUMICEF	IL-17R; Human IgG2	Psoriasis	In review	In review
Guselkumab	(Pending)	IL-23 p19; Human IgG1	Plaque psoriasis	In review	In review
Romosozumab	(Pending)	Sclerostin; Humanized IgG2	Osteoporosis in postmenopausal women at increased risk of fracture	NA	In review

*Data as of December 1, 2016; #Brodalumab was approved in Japan on July 4, 2016; a comprehensive table of approved antibody therapeutics and those in regulatory review in the EU or US is maintained on The Antibody Society's website (www.antibodysociety.org).

Abbreviations: ADC, antibody-drug conjugate; CD, cluster of differentiation; IL, interleukin; NA, not in review in the EU, information on review status in US not available; PD-L1, programmed death ligand 1.

Inotuzumab ozogamicin is a humanized IgG4 anti-CD22 antibody-drug conjugate (ADC). The molecule comprises calicheamicin, which binds DNA in the minor groove and causes strand breaks, conjugated to inotuzumab via a cleavable linker. A marketing authorization application for acute lymphocytic leukemia (ALL) is being reviewed by EMA. The ADC has orphan drug designation in the EU for this indication. Results of the Phase 3 INO-VATE ALL study (NCT01564784) evaluating the safety and efficacy of inotuzumab ozogamicin compared with investigator-choice chemotherapy in 326 adult patients with relapsed or refractory CD22-positive ALL showed improvement over chemotherapy on a number of measures, including complete hematologic remission and progression-free survival.¹⁴ Inotuzumab ozogamicin was granted Breakthrough Therapy and orphan drug designations by FDA for ALL.

Dupilumab (Dupixent[®]), an anti-IL-4R α IgG4 mAb, is undergoing review by EMA and FDA for atopic dermatitis. The mAb has Breakthrough Therapy designation for this indication, and the BLA was granted a priority review. FDA's action date for the application is March 29, 2017. In the Phase 3 SOLO 1 (NCT02277743) and SOLO 2 (NCT02277769) studies, which had identical design and included a total of 1379 patients, dupilumab improved the signs and symptoms of atopic dermatitis compared with placebo.¹⁵

Sirukumab is a human anti-IL-6 mAb being evaluated by EMA, FDA and the Ministry of Health, Labor and Welfare in Japan for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA). Data from the Phase 3 SIRROUND program, which included five studies (SIRROUND-D, SIRROUND-T, SIRROUND-H, SIRROUND-M and SIRROUND-LTE), served as the basis for submission of the marketing applications. In SIRROUND-H (NCT02019472), patients administered 50 mg sirukumab every 4 weeks and patients administered 100 mg sirukumab every 2 weeks experienced significant mean changes from baseline in their Disease Activity Score (DAS28) at week 24 (−2.58 and −2.96, respectively), compared with a mean change of −2.19 in patients administered 40 mg adalimumab every 2 weeks ($P = 0.013$ and $P < 0.001$, respectively). In SIRROUND-T (NCT01606761), patients refractory or intolerant to one or more anti-tumor necrosis factor treatments receiving sirukumab demonstrated significant improvement in signs and symptoms of active RA compared with patients who received placebo.¹⁶

Sarilumab, a human IgG1 targeting IL-6R, is undergoing review by EMA, FDA and the Ministry of Health, Labor and Welfare in Japan for the treatment of adult patients with moderately to severely active RA. The BLA submitted to FDA has undergone a first review. On October 28, 2016, Sanofi and Regeneron Pharmaceuticals announced that FDA had issued a Complete Response Letter regarding the BLA. FDA identified deficiencies during a routine good manufacturing practice inspection of the Sanofi Le Trait facility where sarilumab is filled and finished. If the deficiencies are suitably addressed, the application may undergo a second review. The marketing applications for sarilumab are based on results from seven Phase 3 trials in the SARILRA clinical development program, including SARIL-RA-MOBILITY, SARIL-RA-TARGET and SARIL-RA-MONARCH. These studies incorporate data from

more than 3,300 adults with moderately to severely active RA. The SARIL-RA-MONARCH study (NCT02332590) enrolled 369 adults with active RA who were inadequate responders to, intolerant of, or inappropriate candidates for methotrexate. Patients received either SC sarilumab monotherapy (200 mg every 2 weeks) or adalimumab monotherapy (40 mg every 2 weeks); patients who did not respond adequately to adalimumab could increase to weekly dosing. The primary endpoint was change from baseline in DAS28-ESR at 24 weeks, which was −3.28 for sarilumab compared with −2.20 for adalimumab, $p < 0.0001$.^{17,18}

Guselkumab (CNTO 1959), an IgG1 mAb that targets the IL-23 p19 subunit, is undergoing review by FDA and EMA as a treatment for plaque psoriasis. The safety and efficacy of guselkumab in psoriasis patients was evaluated in three Phase 3 studies, VOYAGE1 and 2 (NCT02207231 and NCT02207244) and NAVIGATE (NCT02203032). The VOYAGE1 and 2 studies assessed the effects of 100 mg SC doses of guselkumab vs Humira[®] (adalimumab) or placebo in patients with moderate to severe plaque psoriasis. Results of the VOYAGE1 study were presented at the 25th European Academy of Dermatology and Venereology Congress held in September 2016.¹⁹ At week 16, significantly higher proportions of patients receiving guselkumab achieved an Investigator's Global Assessment score of cleared or minimal disease and at least a 90 percent improvement in the Psoriasis Area Severity Index (85.1% and 73.3%, respectively) compared with those taking Humira[®] (65.9% and 49.7%, respectively). The values for these endpoints were also significantly higher in patients who received guselkumab vs placebo. Findings from VOYAGE2 and the NAVIGATE study, which evaluated the efficacy and safety of guselkumab for the treatment of subjects with moderate to severe plaque-type psoriasis and an inadequate response to ustekinumab, have not yet been released.

Romozosumab is a humanized IgG2 mAb targeting sclerostin. A BLA for romozosumab for treatment of osteoporosis in postmenopausal women at increased risk of fracture is undergoing review by FDA. The application received a standard review, and FDA's action date is July 19, 2017. The BLA includes data from the placebo-controlled Phase 3 FRAME study (NCT01575834) in which ~7,200 patients received either 210 mg romozosumab SC administered monthly or placebo SC monthly for the 12-month double-blind study period. Patients then entered the open-label phase in which all patients received 60 mg denosumab SC every six months for 12 months. In the FRAME study, romozosumab significantly reduced the incidence of new vertebral fractures in postmenopausal women with osteoporosis through 12 and 24 months.²⁰ The safety and efficacy of romozosumab is also being evaluated in clinical studies of men with osteoporosis.

Antibodies that may enter regulatory review in late 2016 or 2017

Based on announcements of company plans for regulatory submissions and the estimated completion dates for Phase 2/3 or 3 studies, and assuming the study results are positive, marketing applications for at least 6 antibody therapeutics (benralizumab, tildrakizumab, emicizumab, galcanezumab, ibalizumab,

PRO-140) that are now being evaluated in late-stage clinical studies may be submitted during December 2016 or 2017.

Benralizumab (MEDI-563) is a glycoengineered anti-IL-5 receptor α IgG1 that induces rapid and nearly complete depletion of eosinophils. The mAb is derived from Kyowa Hakko Kirin's POTELLIGENT[®] FUT8-knockout Chinese hamster ovary cells, which yield afucosylated antibodies.²¹ Benralizumab has been evaluated as a treatment for asthma in 5 Phase 3 studies that are completed, and it is being evaluated in 4 additional Phase 3 studies of asthma patients that are on-going as of November 1, 2016. The results of two Phase 3 studies, SIROCCO and CALIMA were recently published.^{22,23} The Phase 3 SIROCCO study (NCT01928771) evaluated the safety and efficacy of benralizumab added to high-dose inhaled corticosteroid plus a long-acting β 2 agonist in patients (12–75 y of age) with severe uncontrolled asthma with eosinophilia.²² Patients were administered 30 mg benralizumab either every 4 weeks (400 patients) or every 8 weeks (398 patients; first three doses every 4 weeks) or placebo every 4 weeks (407 patients) for 48 weeks as add on to their standard treatment. Asthma symptoms were improved when benralizumab was given every 8 weeks, but not every 4 weeks, compared with placebo. Both benralizumab dose regimens reduced the annual asthma exacerbation rate over 48 weeks (rate ratio 0.55, 95% CI 0.42–0.71; $p < 0.0001$ for 4 week and 0.49, 0.37–0.64; $p < 0.0001$ for 8 week schedule, respectively) compared with placebo.²²

The Phase 3 CALIMA study (NCT01914757) evaluated the efficacy and safety of benralizumab in asthmatic adults and adolescents inadequately controlled on inhaled corticosteroid plus long-acting β 2 agonist.²³ During the study period of 56 weeks, patients received 30 mg benralizumab either every 4 weeks (425 patients) or every 8 weeks (441 patients), or placebo (440 patients). Annual exacerbation rates were significantly lower for patients who received benralizumab on either the 4 week (rate 0.60 [95% CI 0.48–0.74], rate ratio 0.64 [95% CI 0.49–0.85], $p = 0.0018$, $n = 241$) or 8 week schedule (rate 0.66 [95% CI 0.54–0.82], rate ratio 0.72 [95% CI 0.54–0.95], $p = 0.0188$, $n = 239$) compared with placebo (rate 0.93 [95% CI 0.77–1.12], $n = 248$).²³ AstraZeneca has indicated that it plans to submit a marketing application for benralizumab before the end of 2016.

Tildrakizumab (MK-3222), an IgG1 mAb targeting IL-23 p19 subunit, is undergoing evaluation in Phase 3 studies as a treatment for psoriasis. Results of a Phase 2b study (NCT01225731) of tildrakizumab in patients with chronic plaque psoriasis were recently reported.²⁴ This study was conducted in 355 adults who were randomized to receive SC doses of tildrakizumab (5, 25, 100, 200 mg) or placebo at weeks 0 and 4 and every 12 weeks thereafter until week 52. Administration of the study drug was discontinued at week 52 and the participants were followed through week 72. At week 16, a 75% skin clearance (Psoriasis Area and Severity Index (PASI) 75) was achieved by 33.3% ($n = 14$), 64.4% ($n = 58$), 66.3% ($n = 59$), 74.4% ($n = 64$) and 4.4% ($n = 2$) of patients in the 5-, 25-, 100- and 200-mg tildrakizumab and placebo groups, respectively ($P \leq 0.001$ for each tildrakizumab dose vs. placebo). The PASI 75 response was generally maintained through week 52, and only 4% (8/222) patients who achieved PASI 75 response at week 52 relapsed during the period drug administration was discontinued.²⁴

Tildrakizumab was evaluated in two Phase 3 studies in which the mAb was administered SC to psoriasis patients at a doses of 100 or 200 mg at week 0 and week 4, and then every 12 weeks until study end or participant discontinuation. The Phase 3 study NCT01729754 was a 52-week active comparator (50 mg etanercept) and placebo-controlled, parallel design study to evaluate the efficacy and safety/tolerability of SC tildrakizumab, followed by an optional long-term safety extension study, in patients with moderate-to-severe chronic plaque psoriasis. Eligible participants could enroll in the extension study with an additional treatment period of up to 192 week, followed by a 20 weeks follow-up period. Enrollment was 1090 patients. The Phase 3 study NCT01722331 was a 64-week study with a similar design, but it did not include an active comparator arm. Enrollment was 772 patients. The primary endpoints of the studies were met.²⁵ In the studies, an average of 63% of patients who were administered 100 mg tildrakizumab achieved a PASI 75 by week 12, and 77% achieved a PASI 75 after 28 weeks. An average of 57% and 66% of patients had a Physician's Global Assessment score of clear or minimal with the 100 mg dose at weeks 12 and 28, respectively. An average of 64% and 78% of patients who were administered 200 mg tildrakizumab achieved PASI 75 at weeks 12 and 28, respectively, with 59% and 69% of the patients showing a PGA score of clear or minimal at those timeframes.²⁵

Emicizumab (ACE910, RG6013, RO5534262) is an asymmetric bispecific IgG4 mAb that binds both Factor IXa and Factor X, thereby replacing the function of Factor VIII.^{26,27} The mAb is manufactured using Chugai's proprietary Asymmetric Re-engineering Technology-Immunoglobulin, which incorporates three bispecific antibody engineering approaches: 1) introduction of a common light chain to reduce the number of combinations of light and heavy chains; 2) introduction of differences in the charges of two heavy chains to facilitate purification of the target bispecific molecule; and 3) use of electrostatic steering of the two heavy chains to facilitate expression of the target bispecific molecule.²⁸

Emicizumab is undergoing evaluation as a treatment for hemophilia A. The current standard of care for hemophilia A is prophylactic and episodic intravenous infusions of Factor VIII, which has a short half-life (8–12 hours). Prophylactic emicizumab administered by SC injection once a week is being evaluated in a Phase 3 study (NCT02622321) of hemophilia A patients with inhibitors who were previously treated with episodic or prophylactic bypassing agents. Patients will receive emicizumab or placebo at doses of 3 mg/kg/week for 4 weeks followed by 1.5 mg/kg/week up to the end of the study. An estimated 118 patients will be enrolled, and the primary completion date of the study is February 2017. The US FDA granted breakthrough therapy designation, which is intended to expedite the development and review of drugs for serious or life-threatening conditions, to emicizumab for the prophylactic treatment of people who are 12 y or older with hemophilia A with Factor VIII inhibitors. Positive results from the NCT02622321 study may enable the submission of a marketing application in 2017.

Galcanezumab (LY2951742), an IgG4 mAb targeting calcitonin gene-related peptide, is undergoing evaluation in studies of patients with headache or migraine. In a placebo-controlled

Phase 2 study (NCT01625988), adult patients with four to 14 migraine headache days per month were administered 150 mg galcanezumab as a SC injection once every 2 weeks for 12 weeks.²⁹ For galcanezumab vs placebo administration, the average change from baseline to week 12 in the number of migraine headache days was -4.2 (62.5% decrease) vs -3.0 (42.3% decrease), respectively.

Galcanezumab is undergoing evaluation in 5 Phase 3 studies with primary completion dates in 2017. The REGAIN study (NCT02614261) is a randomized, double-blind, placebo-controlled study of galcanezumab in patients with chronic migraine. The mAb is given by SC injection once a month for 3 months, and the primary outcome measure is the mean change from baseline in the number of monthly migraine headache days. The estimated enrollment for the study is 825 patients; the primary completion date is February 2017.

In the EVOLVE-1 (NCT02614183) and EVOLVE-2 (NCT02614196) studies, galcanezumab will be evaluated for prevention of episodic migraine. In both studies, galcanezumab is given by SC injection once a month for 6 months, and results will be compared with patients who received placebo. The primary outcome measure is the mean change from baseline in the number of monthly migraine headache days, and the estimated enrollment is 825 patients for each of the two studies. The primary completion dates are February 2017 and June 2017 for EVOLVE-1 and EVOLVE-2, respectively.

In the Phase 3 NCT02438826 randomized, double-blind, placebo-controlled study of galcanezumab in patients with chronic cluster headache, the mAb is administered by SC injection every 30 d for 12 weeks, then every 30 d for 12 months during a long-term open label extension of the study. The primary outcome measure is mean change from baseline in weekly cluster headache attack frequency. The estimated enrollment is 162 patients, and the primary completion date is May 2017. Galcanezumab is also undergoing evaluation in the Phase 3 NCT02614287 open-label study to evaluate the longer term safety of the drug in patients with episodic or chronic migraine with or without aura. In this study, galcanezumab is given by SC injection once a month for up to 12 months, and the primary outcome measure is percentage of participants who discontinue. The estimated enrollment is 250 patients, and the primary completion date is September 2017. Eli Lilly, sponsor of the galcanezumab studies, has noted that marketing applications for galcanezumab in episodic and chronic cluster headache or migraine may occur in 2017.³⁰

Ibalizumab, an anti-CD4 IgG4 mAb, is undergoing evaluation as a treatment for human immunodeficiency virus (HIV)-1 infection. The mAb binds to the second extracellular domain of CD4, thereby blocking the virus but maintaining normal immunological functions of CD4+ immune cells. The FDA has granted ibalizumab Fast Track, Breakthrough Therapy, and orphan drug designations. Ibalizumab plus an optimized background regimen (OBR) is being evaluated in the Phase 3 TMB-301 study (NCT02475629) of treatment-experienced patients infected with multi-drug resistant HIV-1. The OBR of antiretroviral medications was selected on the basis of treatment history and the results of screening viral resistance and tropism testing. The study comprises three periods: 1) a control period (Days 0–6) during which patients are monitored on current

failing therapy (or no therapy, if the patient has failed and discontinued treatment within the 8 weeks preceding screening); 2) an essential monotherapy period (Days 7–13) during which patients continue on current failing therapy and receive one intravenous (IV) 2000 mg dose (loading dose) of ibalizumab on Day 7; and 3) a maintenance period (Day 14–Week 25) during which the OBR, which must include at least one agent to which the patient's virus is susceptible, is initiated; beginning at Day 21, 800 mg of ibalizumab are administered every 2 weeks through Week 23. The primary efficacy endpoint is the proportion of patients achieving a ≥ 0.5 log₁₀ decrease in HIV-1 RNA seven days after initiating ibalizumab therapy, day 14 of the study. A total of 40 patients have been enrolled in the study. Results reported in October 2016 indicate that patients experienced a significant decrease in viral load after receiving the loading dose of ibalizumab in addition to their failing antiretroviral therapies (or no therapy). The average decrease in viral load was 1.1 log₁₀, with 83% (33/40) and 60% of patients achieving a ≥ 0.5 log₁₀ and ≥ 1.0 log₁₀ decrease, respectively.³¹ Theratechnologies Inc. and its partner, TaiMed Biologics, Inc., have indicated that the Phase 3 study is the last pivotal clinical study necessary for the completion of a BLA, although patients who completed treatment in the TMB-301 study are offered participation in the TMB-311 expanded access study (NCT02707861).

PRO140 is a humanized IgG4κ mAb targeting the chemokine receptor CCR5, which is expressed on macrophages, dendritic cells and memory T cells, as well as other cell types. During HIV infection, CCR5 acts as a co-receptor for entry of the virus. PRO140 specifically inhibits CCR5-tropic (R5) type 1 HIV. The Phase 2b/3 two-part study (NCT02483078), will evaluate the efficacy, safety, and tolerability of PRO-140 in conjunction with existing antiretroviral therapy (ART) (failing regimen). In this study, PRO140 (350 mg) is administered weekly SC with existing ART for one week. After one week, all subjects enter the 24-week single-arm, open-label treatment period. During this period, all patients receive PRO140 SC injection and OBR. Responses of patients who receive PRO-140 and OBR will be compared with those of patients who received placebo and OBR. The primary outcome measure is the proportion of patients with ≥ 0.5 log₁₀ reduction in HIV-1 RNA viral load from baseline at the end of the 1-week double-blind treatment period. Secondary outcome measures include percentage of participants achieving HIV-1 RNA < 400 copies/mL and < 50 copies/mL, mean change from baseline in HIV-1 RNA levels (log₁₀ copies/mL), and mean change from baseline in CD4 cell count at week 25 for all patients and within each stratum. The estimated enrollment is 30 patients, and the estimated primary completion date is August 2017. PRO-140 received FDA's Fast Track designation; CytoDyn has indicated that a rolling BLA submission is expected in 2017.³²

Antibodies in Phase 3 studies with completion dates in late 2016 or during 2017: Cancer indications

A total of 20 investigational mAbs for cancer indications are currently in late-stage clinical studies (Table 3). Of these, 5 mAbs (durvalumab, JNJ-56022473, ublituximab, anetumab ravtansine, glembatumumab vedotin) are undergoing

Table 3. Monoclonal antibodies in late-stage clinical studies for cancer indications.

Primary sponsoring company	INN or code name	Molecular format	Target(s)	Most advanced phase	Pivotal Phase 2, Phase 2/3 or 3 indications
Actinium Pharmaceuticals	I-131-BC8, lomab-B	Murine IgG1, radio-labeled	CD45	Phase 3	Ablation of bone marrow prior to haematopoietic cell transplantation in AML patients
Janssen Seattle Genetics	JNJ-56022473, CSL362 Vadastuximab talirine	Humanized mAb IgG1 ADC	IL-3R α (CD123) CD33	Phase 2/3 Phase 3	Acute myeloid leukemia Acute myeloid leukemia
TG Therapeutics	Ublituximab	Chimeric IgG1	CD20	Phase 3	Chronic lymphocytic leukemia
AstraZeneca/ MedImmune LLC	Moxetumomab pasudotox	Murine IgG1 dsFv immunotoxin	CD22	Phase 3	Hairy cell leukemia
Xencor	XMAB-5574, MOR208	Humanized IgG1	CD19	Phase 2/3	Diffuse large B-cell lymphoma
Viventia Bio	Oportuzumab monatox	Humanized scFv immunotoxin	EpCAM	Phase 3	Bladder cancer
MacroGenics	Margetuximab	Chimeric IgG1	HER2	Phase 3	Breast cancer
Merrimack Pharmaceuticals	MM-302	scFv-targeted liposome containing doxorubicin	HER2	Phase 2/3	Breast cancer
Immunomedics, Inc.	Sacituzumab govitecan	IgG1 ADC	TROP-2 (epithelial glyco-protein-1)	Phase 3	Triple-neg. breast cancer
Celldex Therapeutics	Glembatumumab vedotin	Human IgG2 ADC	Glyco-protein NMB	Pivotal Phase 2	Triple-neg. breast cancer
Gilead Sciences	Andecaliximab	Humanized IgG4	MMP9	Phase 3	Gastric cancer or gastroesophageal junction adenocarcinoma
AbbVie	Depatuxizumab mafodotin	IgG1 ADC	EGFR	Phase 2/3	Glioblastoma
AstraZeneca/ MedImmune LLC	Durvalumab	Human IgG1	PD-L1 (CD274)	Phase 3	Non-small cell lung, head and neck, bladder, triple-neg. breast, urothelial cancers
AstraZeneca/ MedImmune LLC	Tremelimumab	Human IgG2	CTLA4	Phase 3	Non-small cell lung, head and neck, urothelial cancer
Recombio SL	Racotumomab	Murine IgG1	GM3	Phase 3	Non-small cell lung cancer
Bayer	Anetumab ravtansine	Human IgG1 ADC	Mesothelin	Pivotal Phase 2	Mesothelioma
ImmunoGen	Mirvetuximab soravtansine	IgG1 ADC	Folate receptor 1	Phase 3	Ovarian cancer
Philogen SPA	L19IL2 + L19TNF	scFv conjugates	Fibronectin extra-domain B	Phase 3	Melanoma
Tracon	Carotuximab	Chimeric IgG1	Endoglin	Phase 3	Angiosarcoma

Note: Data updated as of December 1, 2016.

Abbreviations: ADC, antibody-drug conjugate; CD, cluster of differentiation; CTLA, cytotoxic T-lymphocyte-associated protein 4; dsFv, disulfide-stabilized variable fragment; EGFR, epidermal growth factor receptor; EpCAM, epithelial cell adhesion molecule; IL, interleukin; MMP, matrix metalloproteinase; PD, programmed death; PD-L1, programmed death ligand 1; scFv, single-chain variable fragment.

evaluation in pivotal Phase 2, Phase 2/3 or Phase 3 studies that have estimated primary completion dates in late 2016 or during 2017. Positive results from these studies may enable submission of marketing applications in 2017 or 2018, or provide justification for additional studies.

Durvalumab (MEDI-4736) is an IgG1 mAb engineered to prevent antibody-dependent cell-mediated cytotoxicity (ADCC).³³ Its target, PD-L1, binds PD-1 and CD80 (which also binds CTLA-4 and CD28), and thereby suppresses the activation of T cells. By blocking the interaction of PD-L1 with PD-1 and CD80, durvalumab may help to overcome the immunosuppressive effects of PD-L1 signaling in anti-tumor T cells. Three Phase 3 studies (ARCTIC, MYSTIC, PACIFIC) evaluating the effects of durvalumab with or without other agents in patients with non-small cell lung cancer (NSCLC) have estimated primary completion dates in late 2016 or during 2017.

The open label, randomized ARCTIC study (NCT02352948) will evaluate durvalumab administered as monotherapy or in combination with anti-CTLA-4 tremelimumab (CP-675,206) versus standard of care in patients with locally advanced or metastatic NSCLC (Stage IIIb-IV) who have received at least

two prior systemic treatment regimens, including one platinum-based chemotherapy regimen, and do not have known epidermal growth factor receptor (EGFR)-activating mutations or anaplastic lymphoma kinase (ALK) rearrangements.³⁴ Patients with PD-L1-positive tumors will receive durvalumab monotherapy (10 mg/kg IV every 2 weeks for up to 12 months) and those with PD-L1-negative tumors will receive the combination of durvalumab plus tremelimumab (durvalumab 20 mg/kg IV every 4 weeks plus tremelimumab 1 mg/kg IV every 4 weeks for up to 12 weeks then durvalumab alone 10 mg/kg IV every 2 weeks for 34 weeks) or either agent as monotherapy (durvalumab monotherapy as above; tremelimumab monotherapy 10 mg/kg IV every 4 weeks for 24 weeks then every 12 weeks for 24 weeks). The primary outcome measures are overall survival and progression-free survival. The estimated enrollment is 730 and the estimated primary completion date is November 2016.

The Phase 3 MYSTIC study (NCT02453282) is evaluating the efficacy and safety of durvalumab plus tremelimumab combination therapy and durvalumab monotherapy vs. platinum-based standard of care chemotherapy in the first-line treatment

of patients with EGFR and ALK wild-type locally advanced or metastatic NSCLC. The primary outcome measures are overall survival and progression-free survival. The estimated enrollment is 1092 and the primary completion date is January 2017. The Phase 3 PACIFIC study (NCT02125461) is evaluating durvalumab as sequential therapy in patients with locally advanced, unresectable NSCLC (Stage III) who have not progressed following definitive, platinum-based, concurrent chemoradiation therapy. The primary outcome measures are overall survival and progression-free survival. The estimated enrollment is 702 and the estimated primary completion date is May 2017.

Durvalumab is also being evaluated in Phase 3 studies of other cancers, including triple-negative breast cancer, HNSCC and bladder cancer. The mAb received FDA's Fast Track designation for the treatment of patients with PD-L1-positive metastatic HNSCC and Breakthrough Therapy designation for the treatment of patients with PD-L1-positive inoperable or metastatic urothelial bladder cancer whose tumor has progressed during or after one standard platinum-based regimen. In early November 2016, FDA placed a partial clinical hold on the enrollment of new patients with HNSCC in clinical trials of durvalumab as monotherapy and in combination with tremelimumab. This action followed AstraZeneca decision to pause enrollment while adverse events related to bleeding in the Phase 3 KESTREL (NCT02551159) and EAGLE (NCT02369874) studies were investigated. The hold was lifted in late November 2016, and enrollment in the studies is expected to proceed.

JNJ-56022473, previously known as CSL362, is an Fc-engineered mAb targeting the IL-3 receptor α -chain (CD123), which is highly expressed on acute leukemia cells. The Fc modification increases the affinity for Fc γ RIIIa (CD16), thereby enhancing ADCC.³⁵ JNJ-56022473 has been shown to induce ADCC against CD123+ acute myeloid leukemia (AML) blasts and leukemic stem cells in vitro and reduce leukemic cell growth in murine xenograft models of human AML.³⁶ The mAb's mechanisms of action^{36,37} may also be relevant in systemic lupus erythematosus.³⁸ Engineered with Xencor's XmAb[®] technology, the mAb was licensed to Janssen by CSL Limited in 2013. Current clinical development is focused on the evaluation of JNJ-56022473 as an AML treatment.

The safety and efficacy of JNJ-56022473 are being evaluated in a 2-part Phase 2/3 study (NCT02472145) of decitabine plus JNJ-56022473 vs. decitabine alone in patients with AML who are not candidates for intensive chemotherapy. Part A of the study will assess the safety of JNJ-56022473 monotherapy and PK/pharmacodynamics profile of the mAb, and confirm the recommended Phase 2 dose (9 mg/kg JNJ-56022473) in participants for whom experimental therapy is appropriate. The complete response rate and overall survival in participants with AML who are not eligible for intense induction chemotherapy and who are randomly assigned to receive decitabine plus JNJ-56022473 or decitabine alone will be assessed in Part B. The estimated enrollment for this study is 406 patients, and the primary completion date is March 2017.

Ublituximab (LFB-R603, TGT-1101) is a chimeric anti-CD20 IgG1 mAb produced in YB2/0 cells. This cell line yields antibodies with low fucose content, and therefore enhanced

ADCC.²¹ TG Therapeutics gained worldwide rights to develop and commercialize ublituximab for all indications, except for France and Belgium, from LFB Biotechnologies, and TG Therapeutics subsequently licensed rights for development in South Korea and Southeast Asia to Ildong Pharmaceutical Co. Ltd. Ublituximab is currently being evaluated in two Phase 3 studies, GENUINE and UNITY-CLL, of patients with chronic lymphocytic leukemia (CLL). The Phase 3 GENUINE study (NCT02301156) is evaluating the addition of ublituximab to ibrutinib compared with ibrutinib alone in previously treated CLL patients with high-risk cytogenetic features. Ublituximab will be administered by IV infusion on Days 1, 8 and 15 followed by maintenance infusions. The primary outcome measures for the study are the overall response rate and progression-free survival. Estimated enrollment is 330 and the estimated primary completion date is October 2017. If the data are positive, TG Therapeutics plans to use the overall response rate data from the trial as the basis for submission of a BLA for accelerated approval for ublituximab, with the progression-free survival assessment intended to support a filing for full approval.

The UNITY-CLL study (NCT02612311) is a randomized Phase 3 study evaluating ublituximab in combination with TGR-1202, an investigational PI3K δ inhibitor, for patients with front line and previously treated CLL. Patients will be randomized into four treatment arms: 1) ublituximab + TGR-1202; 2) ublituximab alone; 3) TGR-1202 alone, and 4) an active control arm of obinutuzumab + chlorambucil. The primary outcome measure is progression free survival. An early interim analysis will assess contribution of each single agent in the ublituximab + TGR-1202 combination regimen, which, if successful, will allow early termination of both single agent arms. A second interim analysis will be conducted following full enrollment into the study. If positive, TG Therapeutics plans to use the data in a submission for accelerated approval. Assuming early termination of the ublituximab and TGR-1202 single agent arms, the study will enroll ~450 patients. The estimated primary completion date of the UNITY-CLL study is September 2018.

Anetumab ravtansine (BAY 94-9343) is a human anti-mesothelin IgG1 mAb conjugated to the maytansinoid tubulin inhibitor DM4 via a cleavable N-succinimidyl 3-(2-pyridyldithio)butyrate (SPDB) linker. The safety and efficacy of anetumab ravtansine is being evaluated in a pivotal Phase 2 study (NCT02610140) in patients with advanced or metastatic pleural mesothelioma overexpressing mesothelin after progression on platinum/pemetrexed-based chemotherapy. This study is designed to support registration of the ADC. Patients will receive anetumab ravtansine 6.5 mg/kg administered as IV infusion over 1 h every 3 weeks until disease progression or treatment withdrawal for any reason or vinorelbine 30 mg/m² administered as an IV infusion over 6 to 10 min every week until disease progression or treatment withdrawal for any reason. The primary outcome measures is progression free survival in a time frame of ~22 months. The estimated enrollment is 210 patients, and the estimated primary completion date is November 2017. Anetumab ravtansine was granted orphan drug designation for malignant pleural mesothelioma in the EU and US.

Glembatumumab vedotin (CDX-011, CR011-vcMMAE) is an anti-glycoprotein NMB (gpNMB) human IgG2 conjugated to monomethyl auristatin E (MMAE) via an enzyme-cleavable linker. gpNMB is overexpressed by multiple tumor types, and this overexpression is associated with shorter metastasis-free survival and reduced overall survival. The ADC is being evaluated in the pivotal Phase 2 METRIC study (NCT01997333) of patients with gpNMB over-expressing triple negative breast cancer. The METRIC study is designed to enable Celldex to apply for registration with positive results for objective response rate or duration of progression-free survival. The study's primary outcome measure is progression-free survival, which is evaluated every 6–9 weeks following treatment initiation. The estimated enrollment is 300 patients, and the estimated primary completion date is December 2016. Glembatumumab vedotin was granted Fast Track designation for metastatic breast cancer by FDA.

Antibodies in Phase 3 studies with completion dates in 2017: Non-cancer indications

A total of 32 investigational mAbs for non-cancer indications are currently in late-stage studies (Table 4). Of these, 15 mAbs (caplacizumab, lanadelumab, roledumab, tralokinumab, risankizumab, SA237, emapalumab, suptavumab, erenumab, eptinezumab, fremanezumab, fasinumab, tanezumab, lampalizumab, brolocizumab) are undergoing evaluation in Phase 2/3 or Phase 3 studies that have estimated primary completion dates in late 2016 or during 2017. Positive results from these studies may enable submission of marketing applications in 2017 or 2018, or provide justification for additional studies.

Caplacizumab (ALX-0081) is a humanized single-variable-domain immunoglobulin (Nanobody) that targets von Willebrand factor, and thereby inhibits the interaction between von Willebrand factor multimers and platelets. In a Phase 2 study (NCT01151423) of 75 patients with acquired thrombotic thrombocytopenic purpura who received SC caplacizumab (10 mg daily) or placebo during plasma exchange and for 30 d afterward, the time to a response was significantly reduced with caplacizumab compared with placebo (39% reduction in median time, $P = 0.005$).³⁹ The double-blind, placebo-controlled, randomized Phase 3 HERCULES study (NCT02553317) study will evaluate the efficacy and safety of caplacizumab treatment in more rapidly curtailing ongoing microvascular thrombosis when administered in addition to standard of care treatment in subjects with an acute episode of acquired thrombotic thrombocytopenic purpura. Patients will receive an initial IV dose of either caplacizumab or placebo followed by daily SC injections for a maximum period of 6 months. The primary outcome measure is the time to platelet count response. The estimated enrollment is 92 patients, and the estimated primary completion date of the study is October 2017. A Phase 3 follow-up study (NCT02878603) for patients who completed the HERCULES study is planned.

Lanadelumab (DX-2930) is a human IgG1 mAb that targets plasma kallikrein, an enzyme that cleaves high molecular weight kininogen to generate the pro-inflammatory peptide bradykinin, which is a potent vasodilator. The serpin C1-inhibitor regulates plasma kallikrein activity, but individuals

deficient in C1-inhibitor exhibit excessive bradykinin generation that can lead to potentially fatal angioedema. In a Phase 1 study (NCT01923207), a single administration of up to 3.0 mg/kg lanadelumab in healthy volunteers was well tolerated and without dose-limiting toxicity.⁴⁰ The safety and efficacy of lanadelumab in preventing acute angioedema attacks in patients with Type I and Type II hereditary angioedema is being evaluated in a Phase 3 randomized, double-blind, placebo-controlled study (NCT02586805). The study has 4 arms in which patients will be SC administered 300 mg lanadelumab every 2 weeks or every 4 weeks, or 150 mg lanadelumab every 4 weeks, or placebo. The primary outcome measure is the number of angioedema attacks per week observed in each lanadelumab treatment arm vs. placebo arm. Estimated enrollment is 108 patients, and the estimated primary completion date is December 2016. The Phase 3 HELP study extension (NCT02741596), an open-label study to evaluate the long-term safety and efficacy of lanadelumab for prevention against acute attacks of hereditary angioedema, is enrolling patients by invitation. The HELP study has an estimated enrollment of 150 and an estimated primary completion date of December 2017. Lanadelumab has EU and US orphan drug designations, as well as Breakthrough therapy and Fast Track designations for hereditary angioedema.

Roledumab (LFB-R593) is a human IgG1 anti-rhesus (Rh)D mAb derived from YB2/0 cells, which yields antibodies with low fucose content, and therefore enhanced ADCC.²¹ The ability of the mAb to eliminate RhD-positive red blood cells (RBCs) is being evaluated in clinical studies. During pregnancy, the difference in RhD status between an RhD-negative mother and an RhD-positive fetus can lead to proliferation of RhD-reactive B cells in the mother. In a subsequent pregnancy with an RhD-positive fetus, these B cells may then produce anti-RhD antibodies that cross the placenta and cause hemolytic disease of the fetus or newborn, which is potentially fatal. Roledumab thus is designed to bind any RhD-positive RBCs entering the maternal circulation and eliminate them before they can stimulate proliferation of RhD-reactive B cells. In a Phase 1 study, roledumab was safe and well tolerated in doses up to 3000 μg administered IV and at 300 μg administered intramuscularly (IM) to healthy RhD-negative volunteers and the terminal elimination half-life was 18–22 d.⁴¹ Roledumab was evaluated in a Phase 2 study (NCT00952575) that compared the efficacy (in terms of clearance of RhD-positive RBCs) and safety of the mAb vs a polyclonal anti-RhD immunoglobulin in 78 healthy RhD-negative volunteers. In this study, the RhD-positive RBCs were exogenously-administered to the volunteers. The aim of the on-going open label Phase 2/3 study (NCT02287896) is to assess the PK profile, safety and the efficacy to prevent RhD alloimmunization of 300 μg roledumab administered IM / IV in RhD-negative pregnant women carrying an RhD-positive fetus. Immunogenicity will also be assessed. The estimated enrollment is 60 women, and the estimated primary completion date is October 2017.

Tralokinumab is an anti-IL-13 IgG4 mAb in development for immune-mediated disorders, including asthma. In the lung, IL13 regulates eosinophilic inflammation, mucus secretion, and airway hyperresponsiveness. In a Phase 2b study (NCT01402986), patients with severe uncontrolled asthma were assigned to one of

Table 4. Monoclonal antibodies in late-stage clinical studies for non-cancer indications.

Primary sponsoring company	INN or code name	Molecular format	Target(s)	Most advanced phase	Phase 2/3 or 3 indications
Abylnx	Caplacizumab	Humanized nanobody	von Willebrand factor	Phase 3	Acquired thrombotic thrombocytopenic purpura
Chugai/ Roche	Emicizumab	Humanized IgG4, bispecific	Factor IXa, Factor X	Phase 3	Hemophilia A
LFB Group	Roledumab	Human IgG1	Rhesus D	Phase 2/3	Rh disease
Shire	Lanadelumab	Human IgG1	Plasma kallikrein	Phase 3	Hereditary angioedema attacks
Prothena Therapeutics Ltd.	NEOD001	Humanized IgG1	Amyloid	Phase 3	Primary systemic Amyloidosis
Omeros Corporation	OMS721	Human mAb	MASP-2	Phase 3	Atypical hemolytic uremic syndrome
Alexion Pharmaceuticals Inc.	ALXN1210	Humanized mAb	C5	Phase 3	Paroxysmal nocturnal hemoglobinuria
AstraZeneca/ MedImmune LLC	Tralokinumab	Human IgG4	IL-13	Phase 3	Asthma
AstraZeneca/ MedImmune LLC	Benralizumab	Humanized IgG1	IL-5 receptor	Phase 3	Asthma; chronic obstructive pulmonary disease
Adienne Pharma & Biotech	Begelomab	Murine IgG2b	Dipeptidyl-peptidase 4 (CD26)	Phase 3	Graft-vs-host disease
Boehringer Ingelheim Pharmaceuticals, AbbVie	Risankizumab	Humanized IgG1	IL-23 p19	Phase 3	Psoriasis
Merck Sharp & Dohme Corp	Tildrakizumab	Humanized IgG1	IL-23 p19 subunit	Phase 3	Psoriasis
AstraZeneca/ MedImmune LLC	Anifrolumab	Human IgG1	IFN α , β , ω receptor 1	Phase 3	Systemic lupus erythematosus
Genentech	Etolizumab	Humanized IgG1	$\alpha 4$ - $\beta 7$ / αE - $\beta 7$ integrin receptor	Phase 3	UC; Crohn's disease
AstraZeneca/MedImmune LLC	Inebilizumab	Humanized IgG1	CD19	Phase 2/3	Neuromyelitis optica and neuromyelitis optica spectrum disorders
Chugai Pharmaceuticals/ Roche	SA237	Humanized IgG2	IL-6R	Phase 3	Neuromyelitis optica and neuromyelitis optica spectrum disorders
NovImmune SA	Emapalumab	Human IgG1	IFN γ	Phase 2/3	Primary Hemophagocytic Lymphohistiocytosis
Kyowa Hakko Kirin	Burosumab	Human IgG1	FGF23	Phase 3	X-linked Hypophosphatemia
TaiMed Biologics Inc.	Ibalizumab	Humanized IgG4	CD4	Phase 3	HIV infection
CytoDyn	PRO-140, PA14	Humanized IgG4	CCR5	Phase 2/3	HIV infection
Regeneron	Suptavumab	Human IgG1	RSV F protein	Phase 3	RSV infection prevention
Biogen	Aducanumab	Human IgG1	Amyloid β	Phase 3	Alzheimer disease
Genentech	Crenelumab	Humanized IgG4	Amyloid β	Phase 3	Alzheimer disease
Hoffmann-La Roche	Gantenerumab	Human IgG1	Amyloid β	Phase 3	Alzheimer disease
Eli Lilly & Company	Galcanezumab	Humanized IgG4	CGRP	Phase 3	Chronic or episodic cluster headache, prevention of chronic or episodic migraine
Alder Biopharmaceuticals	Eptinezumab	Humanized IgG1	CGRP	Phase 3	Episodic migraines
Teva	Fremanezumab	Humanized IgG2	CGRP	Phase 3	Preventive treatment of migraine (episodic or chronic)
Amgen	Erenumab	Human IgG2	CGRP receptor	Phase 3	Migraine
Regeneron Pharmaceuticals	Fasinumab	Human IgG4	Nerve growth factor	Phase 3	Pain due to osteoarthritis of knee or hip, low back pain
Pfizer; Eli Lilly & Company	Tanezumab	Humanized IgG2	Nerve growth factor	Phase 3	Pain due to osteoarthritis of knee or hip, low back pain, cancer pain due to bone metastasis
Genentech	Lampalizumab	Humanized IgG1 Fab	Factor D	Phase 3	Geographic atrophy associated with dry age-related macular degeneration
Novartis Pharmaceuticals Corp.	Brolucizumab	Humanized scFv	VEGF-A	Phase 3	Neovascular age-related macular degeneration

Note: Data updated as of December 1, 2016.

Abbreviations: CCR, chemokine receptor; CD, cluster of differentiation; CGRP, calcitonin gene-related peptide; Fab, antigen-binding fragment; FGF, fibroblast growth factor; HIV, human immunodeficiency virus; IFN, interferon; IL, interleukin; MASP, mannose-binding protein-associated serine protease; RSV, respiratory syncytial virus; scFv, single-chain variable fragment; VEGF, vascular endothelial growth factor.

two dosing regimen groups (every 2 weeks, or every 2 weeks for 12 weeks then every 4 weeks), then were randomized to receive tralokinumab 300 mg or placebo for 1 y. Asthma exacerbation rates were not significantly reduced in either group, but forced expiratory volume in 1 s showed improvement with tralokinumab given every 2 weeks, and post-hoc subgroup analyses suggested a possible treatment effect. Periostin and DPP-4 were identified as predictors of an enhanced response to tralokinumab.⁴²

Tralokinumab is currently being evaluated in four Phase 3 studies of adults and adolescents (12 to 75 years) with asthma, STRATOS 1 and 2 (NCT02161757 and NCT02194699), TROPIS (NCT02281357), and the Phase 3 NCT02902809 study. All four studies have primary completion dates in 2017. STRATOS 1 and 2 are designed to provide confirmatory evidence of the efficacy and safety of tralokinumab in patients with uncontrolled asthma, and to confirm that periostin and DPP-4 are predictors of an enhanced response to tralokinumab.⁴³

STRATOS1 is a 52-week, randomized, double-blind, parallel group, placebo-controlled, Phase 3 study to evaluate the efficacy and safety of tralokinumab in adults and adolescents with asthma inadequately controlled on inhaled corticosteroid plus long-acting $\beta 2$ -agonist. Patients will receive 300 mg tralokinumab administered SC every 2 weeks or placebo. The primary outcome measure of the study is asthma exacerbation rate reduction. The estimated enrollment is 1140, and the estimated primary completion date is February 2017. STRATOS2 has a similar design. It is a randomized, double-blind, parallel group, placebo-controlled study designed to evaluate efficacy and safety of tralokinumab patients with uncontrolled asthma on inhaled corticosteroid plus long-acting $\beta 2$ -agonist and having a history of asthma exacerbations. Approximately 770 patients will receive 300 mg tralokinumab or placebo, administered via SC injection over a 52-week treatment period. The estimated primary completion date of the study is May 2017.

The placebo-controlled Phase 3 TROPOS study will evaluate the efficacy and safety of a fixed 300 mg dose of tralokinumab administered SC every 2 weeks in reducing oral corticosteroid use in adults and adolescents with oral corticosteroid-dependent asthma. The treatment period is 40 weeks. The primary outcome measure is percent change from baseline in the daily, average, oral corticosteroid dose at week 40 post randomization while not losing asthma control. The estimated enrollment is 120, and the estimated primary completion date is July 2017. The 52-week open label Phase 3 NCT02902809 study will evaluate the safety of tralokinumab in Japanese adults and adolescents with asthma inadequately controlled on inhaled corticosteroid plus long-acting β 2-agonist. Approximately 26 Japanese subjects will be recruited to receive fixed 300 mg SC doses of tralokinumab every 2 weeks during the treatment period. The estimated primary completion date of this study is December 2017.

Risankizumab (ABBV066, BI 655066) is an IgG1 mAb that targets the IL-23 p19 subunit. The mAb is being developed by Boehringer Ingelheim and AbbVie as a potential treatment for immunological disorders, including Crohn's disease, psoriasis and psoriatic arthritis, with AbbVie leading future development and commercialization. Risankizumab is undergoing evaluation as a treatment for psoriasis in four Phase 3 studies with primary completion dates in late 2016 or during 2017. Two of these studies, UltIMMa-1 and -2 (NCT02684370 and NCT02684357, respectively) are evaluating risankizumab vs. ustekinumab and placebo comparators in patients with moderate to severe plaque type psoriasis. The primary outcome measures are achievement of $\geq 90\%$ reduction from baseline score (PASI 90) at week 16 and achievement of a static Physician Global Assessment (sPGA) score of clear or almost clear at week 16. Estimated enrollment for each study is 500 patients, and the estimated primary completion dates are December 2017 for UltIMMa-1 and November 2017 for UltIMMa-2. FDA has granted an orphan drug designation to risankizumab for the investigational treatment of Crohn's disease in pediatric patients.

SA237 is a humanized IgG2 mAb that targets the anti-IL-6 receptor, thereby blocking it from binding the pro-inflammatory cytokine IL-6. Derived from Chugai's proprietary antibody-recycling technology,^{28,44} the mAb is designed to have pH-dependent binding to IL-6R, allowing it to release bound IL-6R in cells and then recycle via the FcRn-mediated antibody recycling pathway. SA237 is undergoing evaluation in two Phase 3 studies of neuromyelitis optica (NMO) and NMO spectrum disorder. SA237 was granted an orphan designation in the EU for the treatment of NMO spectrum disorders, and it received orphan drug designation in the US for treatment of NMO and NMO spectrum disorder.

The randomized, double-blind, placebo-controlled Phase 3 study NCT02028884 will evaluate the efficacy and safety of SA237 added to baseline treatment in patients with NMO and NMO spectrum disorder. The primary outcome measure is the time to first relapse up to ~ 30 months from the entry of the first patient into the study. The estimated enrollment is 70 and the estimated primary completion date is August 2016. The randomized, double-blind, placebo-controlled Phase 3 study NCT02073279 will evaluate the efficacy and safety of SA237 as

monotherapy in patients with NMO and NMO spectrum disorder. The primary outcome measure is the time to first relapse up to ~ 27 months from the entry of the first patient into the study. The estimated enrollment is 90 and the estimated primary completion date is October 2017.

Emapalumab (NI-0501), which targets interferon gamma, is being developed as a potential treatment for primary hemophagocytic lymphohistiocytosis (PHL). This life-threatening condition is characterized by the overwhelming activation of normal T lymphocytes and macrophages. Emapalumab was granted a PRiority MEDicines (PRIME) designation by EMA. The PRIME scheme focuses on medicines that may offer a major therapeutic advantage over existing treatments, or benefit patients without treatment options. In this voluntary scheme, EMA offers early, proactive and enhanced support to developers to optimize the generation of robust data on a medicine's benefits and risks, and enable accelerated assessment of medicine applications. Early clinical data that shows a medicine has the potential to benefit patients with unmet medical needs must be provided for it to be accepted for PRIME access. Emapalumab also has FDA's Breakthrough Therapy Designation, as well as orphan drug designations in the EU and US.

An open-label, single arm Phase 2/3 study (NCT01818492) to explore the safety, tolerability, PK and efficacy of multiple IV administrations of emapalumab in children (up to 18 y old) with PHL is currently recruiting patients. The starting dose was 1 mg/kg, and the initial interval between doses was 3 d. Subsequent dose/interval adjustments were made based on real-time PK monitoring and clinical assessments. Preliminary results have shown emapalumab is well tolerated and has the potential to improve or resolve relevant clinical and laboratory abnormalities of the disease.⁴⁵ The primary outcome measure is the overall response rate. The study has an estimated enrollment of 32 patients, and the estimated primary completion date is December 2016. The long-term safety profile of patients who previously received at least one dose of emapalumab is being assessed in study NCT02069899, which has an estimated primary completion date of December 2017.

Suptavumab (REGN2222) targets the F protein of respiratory syncytial virus (RSV). In a Phase 1 study, suptavumab was generally well tolerated in healthy adults, and the mean-terminal half-life was 32.0+8.79 and 34.4+11.9 d following IM administration of 3 and 10 mg/kg, respectively.⁴⁶ The randomized, double-blind, placebo-controlled Phase 3 NCT02325791 study will evaluate the efficacy, safety, PK, and immunogenicity of REGN2222 in infants born no more than 35 weeks gestational age, who are no more than 6 months of age at the time of enrollment in their respective geographic location. Part A of the study is an open-label, evaluation of the PK of IM administered suptavumab in preterm infants for whom palivizumab is not recommended to enable the selection of dosing regimens for Part B. Part B of the study is randomized, double-blind, and placebo-controlled, designed to evaluate efficacy, safety, serum concentration and immunogenicity of IM administration of suptavumab in preterm infants for whom palivizumab is not recommended. The total duration of Part B will be up to 265 d (includes a 28-day screening period, 57-day treatment period and 180-day follow-up period). For Part A, the primary outcome measure is the serum concentration of REGN2222 from

day 1 through day 150, and for Part B the primary outcome measure is the proportion of participants with a medically attended RSV infection (hospitalization or outpatient lower respiratory tract infection). The estimated enrollment is 1538, and the estimated primary completion date is September 2017.

Erenumab (AMG 334) is an IgG2 mAb that targets the receptor for calcitonin gene-related peptide, a 37-amino acid peptide involved in the development of sensitized primary and secondary nociceptive neurons. The mAb is being co-developed by Amgen and Novartis. Top-line results of the Phase 3 ARISE study (NCT02483585) were announced in September 2016.⁴⁷ In the ARISE study, 577 patients who experienced between 4–14 migraine days each month, with mean of eight migraine days per month at baseline, received either placebo or 70 mg AMG 334 SC once monthly. Patients who received erenumab experienced a statistically significant 2.9-day reduction from baseline in monthly migraine days, as compared with a 1.8-day reduction for those who received the placebo. Top-line results for the Phase 3 STRIVE study (NCT02456740) of erenumab administration to patients with episodic migraine were reported in November 2016.⁴⁸ In this study, 955 patients received once-monthly SC placebo or erenumab (70 mg or 140 mg) for 6 months. The primary endpoint of the study, statistically significant reductions from baseline in monthly migraine days in patients with episodic migraine, was met. At baseline, patients experienced an average of 8.3 migraine days per month. Patients in the erenumab 70 mg and 140 mg treatment arms experienced reductions of 3.2 and 3.7 d from baseline in monthly migraine days, respectively, compared with a 1.8-day reduction in the placebo arm. Amgen has indicated that an application submission is anticipated in 2017.

Eptinezumab (ALD403), an IgG1 mAb that targets the calcitonin gene-related peptide, is in development for migraine. Results of the Phase 2 study NCT02275117 were presented at the 5th European Headache and Migraine Trust International Congress in September 2016.⁴⁹ A total of 616 adult (18–55 y old) patients with a diagnosis of migraine, and ≥ 15 headache days per month of which ≥ 8 d were assessed as migraine days with at least 5 migraine attacks, were randomized and received either a single infusion of eptinezumab 300 mg, 100 mg, 30 mg, 10 mg or placebo by a one hour IV infusion. The drug was well tolerated. For the 300 mg and 100 mg doses, the primary endpoint was met, with a significant number of patients achieving a $\geq 75\%$ reduction in their migraine days (weeks 1–12) vs. placebo. The 300 mg, 100 mg, and 30 mg eptinezumab doses demonstrated a significant difference from placebo for mean change from baseline in migraine days per month (weeks 1–12), and the 300 mg, 100 mg, 30 mg, and 10 mg eptinezumab doses significantly reduced the number of severe migraines reported by patients relative to placebo (weeks 1–12).⁴⁹

The ongoing double-blind, randomized, placebo-controlled, Phase 3 PROMISE 1 study (NCT02559895) is evaluating the efficacy and safety of eptinezumab IV administered once every 12 weeks in ~ 800 patients with frequent episodic migraines. The primary outcome measure is the responder rate at 12 weeks. Alder BioPharmaceuticals, Inc. expects top-line PROMISE 1 data readout in the first half of 2017. A second pivotal study to evaluate the safety and efficacy of eptinezumab in patients with chronic migraine, PROMISE 2, began in

November 2016. The study will enroll $\sim 1,050$ patients randomized to either one of two dose levels of eptinezumab or placebo administered IV once every 12 weeks. The PROMISE 2 study primary endpoint will be the mean reduction in migraine days from baseline over weeks 1 to 12. The company's planned timing for the submission of BLA to the FDA is the second half of 2018.

Fremanezumab (TEV-48125), an IgG2 mAb that targets calcitonin gene-related peptide, is in development for chronic migraine or episodic migraine. In a placebo-controlled Phase 2b study (NCT02021773) of two dose levels of fremanezumab, patients with chronic migraine demonstrated a significant improvement within 1 week of therapy initiation.⁵⁰ Patients administered fremanezumab received either 900 mg as 4 active injections of 225 mg/1.5 mL once monthly, or an initial loading dose of 675 mg (3 active injections of 225 mg and one placebo injection), followed by maintenance doses of 225 mg (one active and 3 placebo injections) for the second and third monthly treatments. Patients receiving placebo received 4 placebo injections monthly. For headache hours, the 675/225-mg dose separated from placebo on day 7 and the 900-mg dose separated from placebo after 3 d of therapy ($p = 0.048$ and $p = 0.033$, respectively).⁵⁰

Fremanezumab is being evaluated in two Phase 3 studies with estimated primary completion dates in 2017. NCT02621931 is a randomized, double-blind, placebo-controlled, parallel-group study comparing the efficacy and safety of 2 dose regimens of SC administration of fremanezumab vs. placebo for the preventive treatment of chronic migraine. Primary outcome measures are the mean change from baseline in the monthly average number of headache days and the percentage of participants with adverse events in a time frame of 12 weeks. The estimated enrollment is 1020 patients, and the estimated primary completion date is September 2017. The similarly designed Phase 3 NCT02629861 study is evaluating the effects of fremanezumab vs. placebo for the preventive treatment episodic migraine. The estimated enrollment is 786 patients, and the estimated primary completion date is September 2017. The long-term safety, tolerability, and efficacy of SC administration of fremanezumab in adult patients with chronic migraine or episodic migraine is being evaluated in a Phase 3 study (NCT02638103) with an estimated primary completion date of September 2018. A Phase 3 study (NCT02945046) of fremanezumab for the prevention of episodic cluster headache is not yet recruiting patients as of early November 2016.

Fasinumab (REGN475), an IgG4 mAb targeting nerve growth factor, is being evaluated in Phase 3 studies as a treatment for moderate-to-severe osteoarthritis pain of the hip or knee, and chronic low back pain. Regeneron Pharmaceuticals, Inc. and Teva Pharmaceutical Industries Ltd. have a global agreement to develop and commercialize fasinumab. The primary endpoint, statistically significant improvement in pain relief, was met in a placebo-controlled Phase 2/3 study (NCT02447276) evaluating fasinumab in patients with moderate-to-severe osteoarthritis pain of the hip or knee who have a history of inadequate pain relief or intolerance to current analgesic therapies.⁵¹ A total of 421 patients were randomized to one of five treatment groups who received fasinumab 1 mg,

3 mg, 6 mg, 9 mg, or placebo, all delivered SC every 4 weeks through week 12, with the primary efficacy measured at week 16. All four treatment groups showed a statistically significant improvement in pain relief. The long-term safety and the efficacy of fasinumab in ~10,000 patients with pain due to osteoarthritis of the knee or hip will be evaluated in the Phase 3 NCT02683239 study, which has an estimated primary completion date of February 2018. Fasinumab is also being evaluated for the treatment of adults with chronic low back pain in the Phase 3 NCT02620020 study, which has an estimated primary completion date of February 2017.

Tanezumab (PF-04383119), an IgG2 mAb targeting nerve growth factor, is being evaluated in Phase 3 studies as a treatment for chronic low back pain, moderate-to-severe osteoarthritis pain of the hip or knee, and pain due to cancer metastasis. As of early November 2016, patients were being recruited for a total of seven Phase 3 studies, including three with estimated primary endpoints in 2017. The placebo-controlled Phase 3 NCT02528253 study will investigate the efficacy and safety of 5 mg and 10 mg doses of tanezumab administered by SC injection seven times at 8 week intervals (total of 56 weeks) for the treatment of chronic low back pain. The primary outcome measure is the change from baseline to week 16 in the daily average low back pain intensity score as measured by an 11 point numeric rating scale for tanezumab vs placebo. The estimated enrollment is 1800, and the estimated primary completion date of the study is May 2017.

The Phase 3 NCT02697773 study will evaluate the efficacy of SC administration of tanezumab in patients with osteoarthritis of the hip or knee. In this study, treatment started at a lower dose (2.5 mg) and increased to a higher dose (5 mg) at Week 8 is compared with giving 2 doses of tanezumab 2.5 mg or 2 doses of placebo. The estimated enrollment is 690, and the estimated primary completion date of the study is July 2017. The Phase 3 NCT02709486 study will evaluate the efficacy of 5 mg and 2.5 mg doses of tanezumab administered SC every 8 weeks vs. placebo at Week 24 in subjects with osteoarthritis of the knee or hip. The primary outcome measures are the Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain subscale, the WOMAC Physical Function subscale, and the Patient's Global Assessment of Osteoarthritis at Week 24. The estimated enrollment is 810, and the estimated primary completion date of the study is November 2017.

Lampalizumab is an antibody antigen-binding fragment (Fab) that targets Factor D, a member of the trypsin family of peptidases and a component of the alternative complement pathway. The Fab is designed to inhibit complement activation and chronic inflammation in tissues. The primary efficacy endpoint of slowing the progression of geographic atrophy lesions in patients with advanced dry age-related macular degeneration was met in the Phase 2 MAHALO study. Lampalizumab showed a 20.4 percent reduction rate in the area of geographic atrophy at 18 months in patients with this type of macular degeneration in this study.⁵² The sham injection-controlled Phase 3 NCT02247531 study will evaluate the efficacy and safety of lampalizumab administered by intravitreal (IVT) injections in patients 50 Years and older with geographic atrophy secondary to age-related macular degeneration. Patients will receive 10-mg dose of lampalizumab administered IVT

every 4 or 6 weeks, or a sham injection. The primary outcome measure is the change in geographic atrophy area, as assessed by retinal imaging, from baseline to Week 48. The estimated enrollment is 936 patients, and the estimated primary completion date of the study is November 2017.

Brolucizumab (RTH258), an antibody single-chain variable fragment that targets vascular endothelial growth factor (VEGF)-A, is being developed as a treatment for neovascular age-related macular degeneration. Two Phase 3 studies of patients with this disorder are active, but not recruiting patients, and both studies have estimated primary completion dates in 2017. The 2-year, 3-arm Phase 3 NCT02307682 study is comparing brolucizumab ophthalmic solution for IVT injection at two dosage levels to aflibercept solution for IVT injection (2 mg/50 μ L) in patients with untreated active choroidal neovascularization secondary to age-related macular degeneration in the study eye. The primary outcome measure is the change in best corrected visual acuity from baseline at Week 48. The estimated enrollment is 1600 patients, and the estimated primary completion date of the study is May 2017. The 2-year, 2-arm Phase 3 NCT02434328 study is comparing the efficacy and safety of brolucizumab solution for IVT injection administered as a 6 mg/50 μ L dose vs. aflibercept administered as a 2 mg/50 μ L dose in patients with neovascular age-related macular degeneration. The primary outcome measure is the change in best corrected visual acuity from baseline at Week 48. The estimated enrollment is 1200 patients, and the estimated primary completion date of the study is June 2017.

Future outlook

The 'Antibodies to watch' article series¹⁻⁹ has documented the recent 100% increase (from 26 mAbs in early 2010 to 52 mAbs in early 2017) in the number of mAbs in Phase 3 clinical studies. With over 230 mAbs currently in Phase 2 clinical studies, the commercial mAb therapeutics pipeline should continue to support a steady flow of mAbs from Phase 2 into Phase 3, as those in Phase 3 advance to regulatory review and to the market. Bispecific mAbs are a promising format to watch in the future. While there is only 1 bispecific mAb currently in Phase 3 studies, 12 are undergoing evaluation in Phase 2 studies and an additional 3 are in Phase 1/2 studies.⁵³

It must be noted, however, that drug development entails risk, and late-stage clinical studies can be terminated due to issues associated with safety, efficacy or quality, or for business reasons such as portfolio management or market changes. For example, in November 2016, Eli Lilly and Company announced that solanezumab did not meet the primary endpoint in the EXPEDITION3 clinical trial of patients with mild dementia due to Alzheimer disease, and regulatory submissions for solanezumab for this indication would not be pursued.⁵⁴ Also in November 2016, Pfizer Inc. announced discontinuation of the global clinical development program for bococizumab, which was in Phase 3 studies of patients with high cholesterol, as a consequence of the evolving treatment and market landscape for lipid-lowering agents.⁵⁵ Despite the challenges, numerous mAbs will undoubtedly enter first pivotal studies or transition from

late-stage development into regulatory review and then on to the market in 2017, and these events will be documented in the next installment of the 'Antibodies to watch' article series.

Note added in proof

On December 9, 2016, AstraZeneca and MedImmune announced that the FDA had accepted a BLA for durvalumab for the treatment of patients with locally advanced or metastatic urothelial carcinoma whose disease has progressed during or after one standard platinum-based regimen. The BLA was granted priority review status and has an action date during the second quarter of 2017. With the addition of durvalumab, Table 2 should thus include a total of 11 mAbs in review in the EU or US as of the end of 2016.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

References

- Reichert JM. Antibodies to watch in 2016. *MAbs* 2016; 8(2):197-204; PMID:26651519; <http://dx.doi.org/10.1080/19420862.2015.1125583>
- Reichert JM. Antibodies to watch in 2015. *MAbs* 2015; 7(1): 1-8; PMID:25484055; <http://dx.doi.org/10.4161/19420862.2015.988944>
- Reichert JM. Antibodies to watch in 2014: Mid-year update. *MAbs* 2014; 6(4):799-802; PMID:24846335; <http://dx.doi.org/10.4161/mabs.29282>
- Reichert JM. Antibodies to watch in 2014. *MAbs* 2014; 6(1):5-14; PMID:24284914; <http://dx.doi.org/10.4161/mabs.27333>
- Reichert JM. Antibodies to watch in 2013: Mid-year update. *MAbs* 2013; 5(4):513-7; PMID:23727858; <http://dx.doi.org/10.4161/mabs.24990>
- Reichert JM. Which are the antibodies to watch in 2013? *MAbs* 2013; 5(1):1-4; PMID:23254906; <http://dx.doi.org/10.4161/mabs.22976>
- Reichert JM. Which are the antibodies to watch in 2012? *MAbs* 2012; 4(1):1-3; PMID:22327425; <http://dx.doi.org/10.4161/mabs.4.1.18719>
- Reichert JM. Antibody-based therapeutics to watch in 2011. *MAbs* 2011; 3(1):76-99; PMID:21051951; <http://dx.doi.org/10.4161/mabs.3.1.13895>
- Reichert JM. Antibodies to watch in 2010. *MAbs* 2010; 2(1):84-100; PMID:20065640; <http://dx.doi.org/10.4161/mabs.2.1.10677>
- US Food and Drug Administration. FDA grants accelerated approval to new treatment for advanced soft tissue sarcoma. October 19, 2016 press release. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm525878.htm>
- Hoffmann-La Roche F. Phase III efficacy results of investigational medicine OCREVUS[®] (ocrelizumab) reinforced by exploratory analyses in two forms of multiple sclerosis. September 14, 2016 press release. <http://www.roche.com/media/store/releases/med-cor-2016-09-14.htm>
- Kaufman HL, Russell J, Hamid O, Bhatia S, Terheyden P, D'Angelo SP, Shih KC, Lebbé C, Linette GP, Milella M, et al. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. *Lancet Oncology* 2016; 17:1374-85; PMID:27592805; [http://dx.doi.org/10.1016/S1470-2045\(16\)30364-3](http://dx.doi.org/10.1016/S1470-2045(16)30364-3)
- XBiotech Inc. XBiotech presents pivotal Phase III data showing XilonixTM demonstrated significant clinical response in advanced colorectal cancer patients refractory to further treatment. July 2, 2016 press release. <http://investors.xbiotech.com/phoenix.zhtml?c=253990&p=irol-newsArticle&ID=2181642>
- Kantarjian HM, DeAngelo DJ, Stelljes M, Martinelli G, Liedtke M, Stock W, Gökbuget N, O'Brien S, Wang K, Wang T, et al. Inotuzumab ozogamicin versus standard therapy for acute lymphoblastic leukemia. *N Engl J Med* 2016; 375:740-53; PMID:27292104; <http://dx.doi.org/10.1056/NEJMoa1509277>
- Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, Silverberg JI, Deleuran M, Kataoka Y, Lacour JP, et al. Two Phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med* 2016 Sep 30; 375:2335-48.
- Janssen. Anti-interleukin-6 monoclonal antibody sirukumab efficacy and safety findings from SIRROUND-H and SIRROUND-T trials presented for the first time at the 2016 ACR/ARHP annual meeting. November 16, 2016 press release. <http://www.janssen.com/new-phase-3-monotherapy-study-sirukumab-versus-humira-and-sirukumab-data-anti-tnf-refractory>
- Regeneron Pharmaceuticals, Inc. Regeneron and Sanofi present results from Phase 3 MONARCH study of investigational sarilumab at American College of Rheumatology annual meeting. November 16, 2016 press release. <http://newsroom.regeneron.com/releasedetail.cfm?ReleaseID=999699>
- Burmester GR, Lin Y, Patel R, van Adelsberg J, Mangan EK, Graham NM, van Hoogstraten H, Bauer D, Ignacio Vargas J, Lee EB. Efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy for the treatment of patients with active rheumatoid arthritis (MONARCH): a randomised, double-blind, parallel-group phase III trial. *Ann Rheum Dis* 2016 Nov 17. pii: annrheumdis-2016-210310. <http://dx.doi.org/10.1136/annrheumdis-2016-210310>. [Epub ahead of print].
- Janssen. New Phase 3 data show significant efficacy versus placebo and superiority of guselkumab versus Humira[®] in treatment of moderate to severe plaque psoriasis. October 1, 2016 press release. www.janssen.com/new-phase-3-data-show-significant-efficacy-versus-placebo-and-superiority-guselkumab-versus-humira
- Cosman F, Crittenden DB, Adachi JD, Binkley N, Czerwinski E, Ferrari S, Hofbauer LC, Lau E, Lewiecki EM, Miyauchi A, et al. Romosozumab treatment in postmenopausal women with osteoporosis. *N Engl J Med* 2016; 375:1532-1543; PMID:27641143; <http://dx.doi.org/10.1056/NEJMoa1607948>
- Beck A, Reichert JM. Marketing approval of mogamulizumab: a triumph for glyco-engineering. *MAbs* 2012; 4:419-25; doi: 10.4161/mabs.20996; PMID:22699226; <http://dx.doi.org/10.4161/mabs.20996>
- Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, Sproule S, Gilmartin G, Aurivillius M, Werkström V, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2 -agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet* 2016; 388:2115-27; [http://dx.doi.org/10.1016/S0140-6736\(16\)31324-1](http://dx.doi.org/10.1016/S0140-6736(16)31324-1)
- FitzGerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M, Ferguson GT, Busse WW, Barker P, Sproule S, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2016; 388:2128-41; [http://dx.doi.org/10.1016/S0140-6736\(16\)31322-8](http://dx.doi.org/10.1016/S0140-6736(16)31322-8)
- Papp K, Thaçi D, Reich K, Riedl E, Langley RG, Krueger JG, Gottlieb AB, Nakagawa H, Bowman EP, Mehta A, et al. Tildrakizumab (MK-3222), an anti-interleukin-23p19 monoclonal antibody, improves psoriasis in a phase IIb randomized placebo-controlled trial. *Br J Dermatol* 2015; 173:930-9; PMID:26042589; <http://dx.doi.org/10.1111/bjd.13932>
- Sun Pharma. Sun Pharma to announce late-breaking results for investigational IL-23p19 inhibitor, tildrakizumab, achieves primary endpoint in both Phase 3 studies in patients with moderate-to-severe plaque psoriasis. October 1, 2016 press release. <http://www.sunpharma.com/media/press-releases>
- Shima M, Hanabusa H, Taki M, Matsushita T, Sato T, Fukutake K, Fukazawa N, Yoneyama K, Yoshida H, Nogami K. Factor VIII-mimetic function of humanized bispecific antibody in hemophilia A. *N Engl J Med* 2016; 374:2044-53; PMID:27223146; <http://dx.doi.org/10.1056/NEJMoa1511769>
- Sampei Z, Igawa T, Soeda T, Funaki M, Yoshihashi K, Kitazawa T, Muto A, Kojima T, Nakamura S, Hattori K. Non-antigen-contacting

- region of an asymmetric bispecific antibody to factors IXa/X significantly affects factor VIII-mimetic activity. *MAbs* 2015; 7:120-8; PMID:25524207; <http://dx.doi.org/10.4161/19420862.2015.989028>
28. Chugai. Chugai's proprietary technologies. <http://www.chugai-pharm.co.jp/profile/pdf/eChugaiProprietaryTechnologies.pdf>
 29. Dodick DW, Goadsby PJ, Spierings EL, Scherer JC, Sweeney SP, Grayzel DS. Safety and efficacy of LY2951742, a monoclonal antibody to calcitonin gene-related peptide, for the prevention of migraine: a phase 2, randomised, double-blind, placebo-controlled study. *Lancet Neurol* 2014; 13:885-92; PMID:25127173; [http://dx.doi.org/10.1016/S1474-4422\(14\)70128-0](http://dx.doi.org/10.1016/S1474-4422(14)70128-0)
 30. Eli Lilly and Company. R&D update for the investment community. May 24, 2016. http://files.shareholder.com/downloads/LLY/1558197365x0x893471/8F87B4E7-9E11-4894-BA1A-446062715EED/LLY_RandD_Update_AM_Session.pdf
 31. Theratechnologies Inc. Phase III study primary endpoint results show ibalizumab significantly reduced viral load in patients with multi-drug resistant HIV-1. October 28, 2016. http://theratech.com/sites/default/files/news_release_en/nr-th-20161028-en.pdf
 32. CytoDyn. PRO140: First self-administered antibody therapy for HIV in late-stage clinical trial. Investor presentation, October 11, 2016. <http://content.equisolve.net/cytodyn/media/a142a8575db88331c0585a336ca2ebfd.pdf>
 33. Stewart R, Morrow M, Hammond SA, Mulgrew K, Marcus D, Poon E, Watkins A, Mullins S, Chodorge M, Andrews J, et al. Identification and characterization of MEDI4736, an antagonistic anti-PD-L1 monoclonal antibody. *Cancer Immunol Res* 2015; 3(9):1052-62; PMID:25943534; <http://dx.doi.org/10.1158/2326-6066.CIR-14-0191>
 34. Planchard D, Yokoi T, McCleod MJ, Fischer JR, Kim YC, Ballas M, Shi K, Soria JC. A Phase III study of durvalumab (MEDI4736) with or without tremelimumab for previously treated patients with advanced NSCLC: Rationale and protocol design of the ARCTIC study. *Clin Lung Cancer* 2016; 17(3):232-236.e1; <http://dx.doi.org/10.1016/j.clc.2016.03.003>
 35. Lazar GA, Dang W, Karki S, Vafa O, Peng JS, Hyun L, Chan C, Chung HS, Eivazi A, Yoder SC, et al. Engineered antibody Fc variants with enhanced effector function. *Proc Natl Acad Sci U S A* 2006; 103(11):4005-10; PMID:16537476; <http://dx.doi.org/10.1073/pnas.0508123103>
 36. Busfield SJ, Biondo M, Wong M, Ramshaw HS, Lee EM, Ghosh S, Braley H, Panousis C, Roberts AW, He SZ, et al. Targeting of acute myeloid leukemia in vitro and in vivo with an anti-CD123 mAb engineered for optimal ADCC. *Leukemia* 2014; 28(3):2213-21; PMID:24705479; <http://dx.doi.org/10.1038/leu.2014.128>
 37. Broughton SE, Hercus TR, Hardy MP, McClure BJ, Nero TL, Dottore M, Huynh H, Braley H, Barry EF, Kan WL, et al. Dual mechanism of interleukin-3 receptor blockade by an anti-cancer antibody. *Cell Rep* 2014; 8(2):410-9; PMID:25043189; <http://dx.doi.org/10.1016/j.celrep.2014.06.038>
 38. Oon S, Huynh H, Tai TY, Ng M, Monaghan K, Biondo M, Vairo G, Maraskovsky E, Nash AD, Wicks IP, et al. A cytotoxic anti-IL-3R α antibody targets key cells and cytokines implicated in systemic lupus erythematosus. *JCI Insight* 2016; 1(6):e86131; PMID:27699260; <http://dx.doi.org/10.1172/jci.insight.86131>
 39. Peyvandi F, Scully M, Kremer Hovinga JA, Cataland S, Knöbl P, Wu H, Artoni A, Westwood JP, Mansouri Taleghani M, Jilma B, et al. Caplacizumab for acquired thrombotic thrombocytopenic purpura. *N Engl J Med* 2016; 374(6):511-22; PMID:26863353; <http://dx.doi.org/10.1056/NEJMoa1505533>
 40. Chyng Y, Vince B, Iarrobino R, Sexton D, Kenniston J, Faucette R, Ten-Hoor C, Stolz LE, Stevens C, Biedenkapp J, et al. A phase 1 study investigating DX-2930 in healthy subjects. *Ann Allergy Asthma Immunol* 2014; 113(4):460-6.e2; <http://dx.doi.org/10.1016/j.ana.2014.05.028>
 41. Yver A, Homery MC, Fuseau E, Guemas E, Dhainaut F, Quagliaroli D, Beliard R, Prost JF. Pharmacokinetics and safety of roledumab, a novel human recombinant monoclonal anti-RhD antibody with an optimized Fc for improved engagement of FC γ RIII, in healthy volunteers. *Vox Sang* 2012; 103(3):213-22; PMID:22568808; <http://dx.doi.org/10.1111/j.1423-0410.2012.01603.x>
 42. Brightling CE, Chaney P, Leigh R, O'Byrne PM, Korn S, She D, May RD, Streicher K, Ranade K, Piper E. Efficacy and safety of tralokinumab in patients with severe uncontrolled asthma: a randomised, double-blind, placebo-controlled, phase 2b trial. *Lancet Respir Med* 2015; 3(9):692-701; PMID:26231288; [http://dx.doi.org/10.1016/S2213-2600\(15\)00197-6](http://dx.doi.org/10.1016/S2213-2600(15)00197-6)
 43. Panettieri RA Jr, Brightling C, Sjobring U, Péterffy A, Tornling G, Daoud SZ, Ranade K, Hollis S, Colice G. STRATOS 1 and 2: considerations in clinical trial design for a fully human monoclonal antibody in severe asthma. *Clin Invest* 2015; 5:701-11; <http://dx.doi.org/10.4155/cli.15.38>
 44. Haraya K, Tachibana T, Iwayanagi Y, Maeda A, Ozeki K, Nezu J, Ishigai M, Igawa T. PK/PD analysis of a novel pH-dependent antigen-binding antibody using a dynamic antibody-antigen binding model. *Drug Metab Pharmacokinet* 2016; 31(2):123-32; PMID:26944099; <http://dx.doi.org/10.1016/j.dmpk.2015.12.007>
 45. Jordan MB, Locatelli F, Allen C, De Benedetti F, Grom A, Ballabio M, Ferlin W, De Min C, on behalf of the NI-0501-04 Study Group. A novel targeted approach to the treatment of hemophagocytic lymphohistiocytosis (HLH) with NI-0501, an anti-IFN γ monoclonal antibody: First results from a pilot Phase 2 study in children with primary HLH. <http://www.novimmune.com/temp/ASH2015Final.pdf>
 46. Sivapalasingam S, Caballero-Perez D, Houghton M, Yang F, Davis J, Gao B, Geba G. Phase I study evaluating safety, tolerability, pharmacokinetics and immunogenicity of REGN2222 in healthy adults: a new human monoclonal RSV-F antibody for RSV prevention. ID Week 2015. Poster Abstract Session: Clinical Trials. October 7-11, 2015, San Diego. <https://idsa.confex.com/idsa/2015/webprogram/Paper53399.html>
 47. Novartis. Novartis announces Phase III study shows AMG 334 significantly reduces monthly migraine days in people with episodic migraine. September 28, 2016 press release. <https://www.novartis.com/news/media-releases/novartis-announces-phase-iii-study-shows-amg-334-significantly-reduces-monthly>
 48. Amgen. Amgen Announces erenumab significantly reduces monthly migraine days in patients with episodic migraine in second phase 3 study. November 16, 2016 press release. <http://www.amgen.com/media/news-releases/2016/11/amgen-announces-erenumab-significantly-reduces-monthly-migraine-days-in-patients-with-episodic-migraine-in-second-phase-3-study/>
 49. Dodick D, Goadsby P, Silberstein S, Lipton R, Chakava G, O'Brien T, Hill R, Krause R, Bonner J, Koltun W, et al. Randomized, double-blind, placebo-controlled trial of ALD403, an anti-CGRP antibody in the prevention of chronic migraine. http://www.alderbio.com/wp-content/uploads/2016/09/Smith-EHMTTC2016poster08Sept2016_FINAL2.pdf
 50. Bigal ME, Dodick DW, Krymchantowski AV, VanderPluym JH, Tepper SJ, Aycardi E, Loupe PS, Ma Y, Goadsby PJ. EV-48125 for the preventive treatment of chronic migraine: Efficacy at early time points. *Neurology* 2016; 87(1):41-8; PMID:27281531; <http://dx.doi.org/10.1212/WNL.0000000000002801>
 51. Regeneron Pharmaceuticals, Inc. Regeneron announces positive topline results from phase 2/3 fasinumab study in patients with osteoarthritis pain. May 2, 2016 press release. http://files.shareholder.com/downloads/REGN/959746525x0x889001/920E5C9C-AA16-4E97-98B7-8EFC55D0BD35/REGN_News_2016_5_2_General_Releases.pdf
 52. Roche. Roche's lampalizumab phase II data shows benefit in patients with the advanced form of dry age-related macular degeneration. August 27, 2013 press release. <http://www.roche.com/investors/updates/inv-update-2013-08-27.htm>
 53. Brinkmann U, Kontermann RE. The making of bispecific antibodies. *MAbs* 2017; 9:in press.
 54. Eli Lilly and Company. Lilly announces top-line results of solanezumab Phase 3 clinical trial. November 23, 2016 press release. <https://investor.lilly.com/releasedetail.cfm?ReleaseID=1000871>
 55. Pfizer Inc. Pfizer discontinues global development of bococizumab, its investigational PCSK9 inhibitor. November 1, 2016 press release. http://www.pfizer.com/news/press-release/press-release-detail/pfizer_discontinues_global_development_of_bococizumab_its_investigational_pcsk9_inhibitor