Therapeutic Indications and Mechanisms of Action in Biologics

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The year 2022 witnessed the control of the COVID-19 pandemic in most countries through social and hygiene measures and also vaccination campaigns. It also saw a decrease in total approvals by the U.S. Food and Drug Administration (FDA). Nevertheless, there was no fall in the Biologics class, which was boosted through the authorization of 15 novel molecules, thus maintaining the figures achieved in previous years. Indeed, the decrease in approvals was only for the category of small molecules. Monoclonal antibodies (mAbs) continued to be the drug class with the most approvals, and cancer remained the most targeted disease, followed by autoimmune conditions, as in previous years. Interestingly, the FDA gave the green light to a remarkable number of bispecific Biologics (four), the highest number in recent years. Indeed, 2022 was another year without the approval of an antimicrobial Biologic, although important advancements were made in targeting new diseases, which are discussed herein. This work analyzes the Biologics authorized in 2022. Furthermore, the orphan drugs authorized was considered. A quantitative analysis was applied to this year's harvest, the efficacy of the Biologics with those authorized in previous years was compared. On the basis of their chemical structure, the Biologics addressed fall into the following classes: monoclonal antibodies; antibody-drug conjugates; and proteins/enzymes.

FDA Biologics anacaulase eflapegrastim

1. Cancer

Of the 15 Biologics approved in 2022, six were indicated for the treatment of a diversity of cancers (**Table 1**). Comparatively, there were four Biologics approved indicated for cancer approved in 2019, eight in 2020, and six in 2021 [1]. From 2019, there has clearly been a growth aimed at cancer in the Biologics market.

Table 1. Biologics for cancer approved by the Food and Drug Administration in 2022.

Trade Name and Active Ingredient	Class	Target/Mechanism of Action	Original Approval Date	Manufacturer	Therapeutic Indication
Kimmtrak™ (tebentafusp) [1] [2][3][4]	Bispecific Fusion Protein	TCR arm binds to gp100 on Uveal Melanoma cells and the anti-CD3 effector binds to T Lymphocytes	25 January 2022	Immunocore Limited	Unresectable or Metastatic Uveal Melanoma

Trade Name and Active Ingredient	Class	Target/Mechanism of Action	Original Approval Date	Manufacturer	Therapeutic Indication
Opdualag™ (nivolumab and relatlimab) [1] [2][5]	Combination of Human mAbs	Blocks LAG-3 and PD-1 receptors from binding to their ligands	18 March 2022	Bristol-Myers Squibb Company	Unresectable or Metastatic Melanoma
Imjudo™ (tremelimumab) [2][6][7]	Human mAb	Binds to CTLA-4	21 October 2022	AstraZeneca AB	uHCC and metastatic NSCLC
Tecvayli™ (teclistamab) [1] [2][8]	Bispecific mAb	CD-3 receptor and BCMA	25 October 2022	Janssen Biotech, Inc.	Multiple Myeloma
Elahere™ (mirvetuximab soravtansine) [2][9]	ADC (chimeric mAb)	IgG1 directed against FRα, releasing DM4	14 November 2022	ImmunoGen, Inc.	PROC, PPC, or Fallopian Tube Cancer
Lunsumio™ (mosunetuzumab) [10][11]	Bispecific mAb	Binds to CD20 and CD3 receptors	22 December 2022	Genentech, Inc.	Relapsed or Refractory Follicular Lymphoma

(+) Orphan Drug; TCR—T-Cell Receptor; gp100—Glycoprotein 100; CD—Cluster of Differentiation; LAG-3—Lymphocyte Activation Gene 3; PD-1—Programmed Death Receptor-1; CTLA-4—Cytotoxic T-Lymphocyte-Associated Antigen 4; uHCC—Unresectable Hepatocellular Carcinoma; NSCLC—Non-Small Cell Lung Cancer; BCMA—B-Cell Maturation Antigen; ADC—Antibody-Drug Conjugate; IgG1—Immunoglobulin G 1; DM4—Antitubulin Agent; FRα—Folate Receptor α; PROC—Platinum-Resistant Epithelial Ovarian Cancer; and PPC—Primary Peritoneal Cancer.

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patients, leading the immune system directly to the cancer cell [3]. One arm of tebentafusp (anti-CD3 effector) binds to T lymphocytes, later dragging the T cell to the cancer cell. This immune cell must bind to glycoprotein 100 (gp100), which may be inside the tumor cell, and therefore needs to be presented to the tumor cell surface through the human leukocyte antigen (HLA). The other arm of tebentafusp (T-cell receptor arm) then targets gp100, binding to the melanoma cell and activating the T cell, which then kills the melanoma cell. Other Biologics have previously been approved for the treatment unresectable or metastatic melanomas, namely Yervoy™ (ipilimumab) in 2011, Keytruda™ (pembrolizumab) and Opdivo™ (nivolumab) in 2014 [12], Tecentriq™ (atezolizumab) in 2016 [1], and Opdualag™ (relatlimab and nivolumab) in 2022. However, tebentafusp is the first Biologic indicated for metastatic uveal melanoma. This type of cancer is very different from other melanomas as it shows distinct patterns, pessimistic prognosis, and a high likelihood of metastasis [13]. These characteristics thus make Kimmtrak™ an important breakthrough. Overall Survival (OS) was the main measure found in the literature for Kimmtrak™, with a median OS of 21.7 months vs. 16 months for the control group [3][13]. For Opdualag™, which is intravenously administered, the main measure found was Progression-Free Survival (PFS) vs. nivolumab alone, with a PFS of 10.1 months for Opdualag™ vs. 4.6 months for nivolumab [5].

As shown in Ref. [14], the combination of mAbs such as Opdualag™ (nivolumab and relatlimab), which was approved this year, offers the interesting advantage of simultaneously targeting multiple pathways. Opdualag™ provides a first-in-class mechanism of action by carrying two fully human mAbs, the first one targeting LAG-3 receptors and the second one PD-1 receptors, thereby increasing T-cell activation [5]. Bispecific mAbs can also target more than one pathway. However, three distinct mAbs can be combined, as is the case of Phesgo™, in which all the mAbs target the glycoprotein (GP) of *Zaire ebolavirus* but in distinct ways. In this regard, between

2015 and 2022, only three combinations of mAbs have received approval, namely the aforementioned Phesgo™ (pertuzumab, trastuzumab, and hyaluronidase) for Ebola vírus, Inmazeb™ (atoltivimab, maftivimab, odesivimab) to treat early or metastatic breast cancer, both approved in 2020 [1], and Opdualag™, which received authorization this year [5].

Of note, the last fusion protein approved by the FDA was in 2018, with tagraxofusp, indicated for the treatment of blastic plasmocytoid dendritic cell neoplasm [1]. While the two cancer drugs tagraxofusp and tebentafusp received Orphan Drug Status, tebentafusp is the first bispecific fusion protein to get the green light to date.

Lunsumio™ (mosunetuzumab), a humanized bispecific mAb, has received accelerated approval from the FDA this year. Indicated to treat a type of non-Hodgkin's lymphoma (relapsed or refractory follicular lymphoma (FL), it presented an Objective Response Rate (ORR) of 80% in clinical trials, with 60% of patients presenting a Complete Response (CR) [11]. Patients affected by follicular lymphoma (FL) have very few treatment options when it comes to Biologics. The other treatment option for this condition is rituximab, which was approved in 1997 and was the first mAb for cancer patients. Its therapeutic indications include FL. In comparison with the new bispecific mosunetuzumab, rituximab has an ORR of around 50% and a CR of 6% [15].

Importantly, from 2015 to 2022, the FDA authorized only four bispecific antibodies, namely emicizumab (2017), amivantamab (2021), faricimab (2022), and mosunetuzumab (2022) [11][16][17][18].

Imjudo™ (tremelimumab) was approved for cancer this year, intravenously administered, indicated for unresectable hepatocellular carcinoma (uHCC) [7]. It is a mAb whose mechanism works by blocking CTLA4, thus stopping the interaction of ligands with the cytotoxic T-lymphocyte-associated antigen 4. The previous cancer Biologic indicated for uHCC to get the green light was Tecentriq™ (atezolizumab)(2016). This Biologic is also a mAb but, in contrast to tremelimumab, it acts by blocking PD-L1 [1]. For uHCC, both drugs are indicated to be used in combination with other mAbs, namely atezolizumab + bevacizumab, and tremelimumab + durvalumab.

In clinical trials, tremelimumab combined with durvalumab, a PD-L1 blocker, demonstrated higher OS (16.43 months vs. control group 13.72 months) and also a better ORR (20.1 vs. 5.1, respectively) [19].

In another advancement by Janssen Biotech Inc., Tecvayli™ (teclistamab), indicated for relapsed or refractory multiple myeloma (MM), was approved in 2022. Importantly, from 2015 to 2021, the FDA authorized five other Biologics for this disease, namely: Darzalex™ (daratumumab) and Empliciti™ (elotuzumab), both in 2015, and Darzalex Faspro™ (daratumumab and hyaluronidase), Sarclisa™ (isatuximab), and the ADC Blenrep™ (belantamab mafodotin), all three in 2020 [1]. Of note, all the Biologics for MM hold Orphan Drug Status.

Belantamab mafodotin (approved in 2020) binds to the B-cell maturation antigen (BCMA), and therefore, has a similar mechanism of action to that of the novel teclistamab. However, the latter is the first bispecific mAb to treat MM. It binds to BCMA and also to CD3 receptors [8]. In clinical trials, teclistamab showed a good ORR, with 40% of the patients presenting a CR [20][21][22].

Intravenously administered, Elahere™ (mirvetuximab soravtansine) was the antibody-drug conjugate (ADC) of 2022 to be approved (fast-track process) by the FDA [23]. This ADC is a FRα-directed (folate receptor alfa) chimeric mAb that targets epithelial ovarian cancer, which has high expression of FRα. When internalized, Elahere™ releases its small molecule (DM4), a microtubule inhibitor, after cleavage of its disulfide linker, unleashing apoptotic cell death. The anti-tubulin agent DM4 is an analog of maytansine, which was last found, before 2022, almost one decade ago in another ADC Kadcyla™ (rastuzumab emtansine) [14]. DM4 is genotoxic, it confers risk to pregnant women, and it is a potent CYP3A4 substrate. Patients treated with DM4 must be closely monitored [9]. From 2015 to 2021, nine ADCs were approved by the FDA [1] and Elahere™ is the tenth of this class.

Regarding efficacy, in a single-arm trial, Elahere™ demonstrated an ORR of 31.7% and a DOR of 6.9 months, but further research is still ongoing [23][24].

Ongoing Clinical Trials for the New Biologics for Cancer

There are trials ongoing for tebentafusp (phase 1b/2) to test this Biologic in metastatic cutaneous melanoma, but in combination with other Biologics (durvalumab and/or tremelimumab), and also tebentafusp alone in advanced non-uveal melanoma, with no results posted yet [25]. Regarding trials for nivolumab and relatlimab to potentially treat diseases other than its primary target, there are trials ongoing to test it in metastatic or unresectable chordoma and [26], a phase 2 trial to test it in advanced microsatellite stable (MSS) colorectal cancer [27], a phase ½ trial to test its effectiveness in liver cancer [28], and interestingly, just like Kimmtrak™ (tebentafusp) mentioned earlier in this paper, whose therapeutic indication is metastatic uveal melanoma (MUM), the first treatment to date specifically for MUM, there is a phase 2 trial ongoing to test nivolumab and relatlimab for MUM [29]. A combination of mAbs such as Opdualag™ carries great potential for repurposing and exploiting new targets/diseases; unfortunately, there are no results posted yet regarding the ongoing trials mentioned.

Tremelimumab is being tested for bladder cancer, with a completion study date in 2026 [30]. It is currently only approved for adult patients, but ongoing studies were found to test tremelimumab in combination with durvalumab in pediatric patients with solid tumors and hematological malignancies [31], and a phase 1 study with a completion date in 2024 for metastatic melanoma [32].

Mirvetuximab soravtansine is being tested as a first-line treatment for triple-negative breast cancer [33], and in combination with pembrolizumab as a new option for endometrial cancer in a phase 2 study, expected to be completed in 2025 [34].

There are trials with mosunetuzumab for four other conditions: reduction of the tumor with mosunetuzumab in combination with polatuzumab vedotin for refractory, relapsed, or aggressive non-Hodgkin lymphoma in a phase 2 study [35]; a phase 1 study to test mosunetuzumab to treat B-cell lymphoma after replacement of patient's stem cells by autologous stem cell transplant [36]; and a phase 1 study assessing the efficacy of mosunetuzumab in relapsed or refractory chronic lymphocytic leukemia (CLL) [37]. All of these three studies have a completion date expected in 2027. There is still a phase 1 study testing mosunetuzumab for systemic lupus erythematosus, with a

completion date expected in 2024 [38]. None of these studies have posted results yet. Regarding teclistamab, ongoing trials were not found for a disease other than multiple myeloma.

2. Autoimmune Conditions

The second type of disease most targeted by the approved Biologics in 2022 is autoimmune conditions (**Table 2**).

Table 2. Biologics approved for autoimmune conditions by the Food and Drug Administration in 2022.

Trade Name and Active Ingredient	Class	Target/Mechanism of Action	Original Approval Date	Manufacturer	Therapeutic Indication
Enjaymo™ (sutimlimab) [1] [2][39]	Humanized mAb	Inhibits the complement pathway and binds to complement protein component 1	4 February 2022	Bioverativ Therapeutics, Inc.	Decrease the need of RBC transfusion due to hemolysis in CAD
Spevigo™ (spesolimab) [1] [2][3][4]	Humanized mAb	IL36R Antagonist	1 September 2022	Boehringer Ingelheim Pharmaceuticals, Inc.	Generalized Pustular Psoriasis Flares
Tzield™ (teplizumab) [2][40][41]	Humanized mAb	Binds to CD3	18 November 2022	Provention Bio, Inc	Delay the onset of Stage 2 or 3 Type 1 Diabetes
Briumvi™ (ublituximab) [42]	Chimeric mAb	Binds to CD20 on B-Cells	28 December 2022	TG Therapeutics, Inc.	Multiple Sclerosis

[1] Orphan Drug; RBC, Red Blood Cell; CAD, Cold Agglutinin Disease; IL36R, Interleukin-36 Receptor; CD, Cluster of Differentiation.

Spevigo™ (spesolimab) has been approved this year to treat generalized pustular psoriasis (GPP), a rare and autoinflammatory condition that can strike both children and adults, affecting more Asians than other population groups [43]. To date, there is no standard treatment specifically for GPP, therapeutic strategies being limited to the use of synthetic drugs and Biologics previously authorized for moderate and severe plaque psoriasis, which have a poor outcome in GPP. As other Biologics indicated to treat plaque psoriasis or psoriatic arthritis have distinct interleukin receptors as targets (i.e., IL-17R), spesolimab brings a new mechanism of action by binding to IL-36R (interleukin-36 receptor), thereby inhibiting IL-36 from binding to IL-36R [4], since GPP seems to have a singular mechanism in its pathogenesis involving the IL-36R [43]. Although further research is needed on this subject, current studies support the efficacy of anti-IL-36R therapy in GPP [43][44][45].

Briumvi™ (ublituximab) (2022) is intravenously administered and it is indicated to treat relapsing forms of multiple sclerosis. Its mechanism of action is like that of Ocrevus™ (ocrelizumab), the previous mAb for multiple sclerosis

approved by the FDA, in 2017. These two drugs bind to CD-20 on B-cells, both pre-B cells and mature B cells, thereby unleashing cell lysis [42][46]. Prior to ocrelizumab, the FDA had only approved Zinbryta™ (daclizumab) (2016) [1], which acts by binding to a subunit of IL-2 receptors, namely CD-25. Between 2015 and 2022, only these three mAbs received the green light for this condition.

In trials, ublituximab has been demonstrated to be superior to an orally administered medication (teriflunomide) in the two endpoints evaluated. In the primary endpoint in trial I, the Annualized Relapse Rate (ARR) reported was 0.08 for ublituximab vs. 0.19 for teriflunomide, and in the same endpoint in trial II, it was 0.09 for ublituximab vs. 0.18 for teriflunomide. In the secondary endpoint in trial I, the average number of gadolinium-enhancing lesions was measured at 0.02 for ublituximab vs. 0.49 for teriflunomide 0.49, and in trial II it was 0.01 for ublituximab vs. 0.25 for teriflunomide, demonstrating lower rates and fewer lesions in the magnetic resonance imaging [47].

Tzield™ (teplizumab) binds to its target CD3 and patients with Stage 2 type 1 diabetes (T1D) can benefit from a delay in the onset of Stage 3. This is a first-in-class and unique treatment that can deactivate certain immune cells involved in T1D. The efficacy of teplizumab in delaying the onset of Stage 3 T1D has been demonstrated in trials. Indeed, the primary measure was time from randomization to the diagnosis of Stage 3 T1D. It was observed that 19.8 (45%) of the patients (of a total of 44) receiving teplizumab had a later diagnosis of Stage 3 TID than the placebo group [40][41][48]. Teplizumab is intravenously administered and it is one of the few Biologics authorized in 2022 for both adult and pediatric patients.

Another important advancement in autoimmune diseases this year is the first-in-class Enjaymo™ (sutimlimab), which is intravenously administered. It is indicated to decrease the need for red blood cells (RBCs) transfusion in cold agglutinin disease (CAD); CAD is a rare condition characterized by the destruction of RBCs in cold temperatures. Sutimlimab also brings a new mechanism of action by binding to the complement protein component 1, inhibiting the complement pathway [39][49]. In a clinical trial, more than half the patients positively responded to sutimlimab by increasing hemoglobin and no RBC transfusion was required after five weeks of treatment, and they reported decreased fatigue [50][51].

Ongoing Clinical Trials for the New Biologics for Autoimmune Conditions

Boehringer Ingelheim is conducting studies to test spesolimab in other conditions. There are trials ongoing to test the efficacy of spesolimab for palmoplantar pustulosis (PPP) in a phase IIa study, with results supporting its efficacy vs. the placebo, but there are still trials ongoing to keep testing for PPP [52][53]. In 2024, a phase 2 study is expected to be completed to test the efficacy of Spesolimab in hidradenitis suppurativa (HS) [54], ulcerative colitis (UC) [55], an improvement of the narrowing of the small bowel in Crohn's disease patients [56], and there are also studies ongoing to test it in atopic dermatitis (AD) and other conditions whose mechanism is similar to those that can cause HC, UC, or AD [57][58].

Ublituximab is being tested in combination with umbralisib for proggressive CLL in a phase 2 trial, and in a phase 1 and 2 study testing tazemetostat in combination with umbrasilib and ublituximab to treat relapsed or refractory

follicular lymphoma [59][60]; no results have been posted yet for either study. Regarding teplizumab and sutimlimab, ongoing trials were not found for diseases other than the primary authorized ones described in the Prescribing Information.

3. Aesthetic

Daxxify™ (daxibotulinumtoxin A) was the Biologic for aesthetic purposes approved by the FDA in 2022 (**Table 3**) and it is administered by intramuscular injection. It is found in the literature as an advancement, considering past decades of the hegemony of Botox™ (onabotulinumtoxin A) to treat glabellar lines. Daxibotulinumtoxin A shows promising results and greater internalization of the neurotoxin, and clinical trials have demonstrated significant differences in response rate and also a longer period of effect for this Biologic. Patients in this trial also showed a better response to this Biologic than to the placebo [61][62][63]. The mean duration of the effects of daxibotulinumtoxin A in clinical trials is around 24 weeks, while for onabotulinumtoxin A it is around 19 weeks [62].

Table 3. Botulinum Toxin A approved by the Food and Drug Administration in 2022.

Trade Name and Active Ingredient	Class	Target/Mechanism of Action	Original Approval Date	Manufacturer	Therapeutic Indication
Daxxify™ (daxibotulinum-toxin A) [2][64]	Botulinum toxin A (protein-based therapy)	Inhibits the release of Acetylcholine to the Neuromuscular Junction	7 September 2022	Revance Therapeutics, Inc.	Improve glabellar lines associated with corrugator and/or procerus muscle activity

The IGA-FWS (Investigator Global Assessment-Facial Wrinkle Severity) and Global Aesthetic Improvement Scale (GAIS) were used to assess the results. Participants in the trial using 40 U of daxibotulinumtoxin A obtained between a 1 and 2 point improvement in glabellar lines, on both scales, over those using 20 U of onabotulinumtoxin A [62][65].

Before 2022, Jeuveau™ (prabotulinumtoxin A) was the last Biologic authorized for aesthetic purposes (2019) [1]. Prabotulinumtoxin A and onabotulinumtoxin A presented similar outcomes in a 3-month study evaluating their effect on crow's feet. The main measure of efficacy for prabotulinumtoxin A vs. onabotulinumtoxin A was mean onset of action (3.81 days for prabotulinumtoxin A vs. 3.47 days for onabotulinumtoxin A) and time to peak effect (9.58 days for prabotulinumtoxin A vs. 11.11 days for onabotulinumtoxin A). The secondary measure was the duration of action (11.11 weeks for prabotulinumtoxin A vs. 11.22 weeks onabotulinumtoxin A) [66]. The literature is still lacking data comparing the novel daxibotulinumtoxin A with prabotulinumtoxin A for the treatment of glabellar lines.

4. Eye Disorders

There have been two important drug advancements for eye disorders in less than three years. In this regard, back in 2019, the single-chain fragment variable (scFv) Beovu™ (brolucizumab), which inhibits three isoforms of VEGF-A, received the green light from the FDA to treat neovascular (Wet) age-related macular degeneration (nAMD) [67]. Two years later, in January 2022, Vabysmo™ (faricimab) (**Table 4**) was also approved for eye disorders such as nAMD and diabetic macular edema (DME). In the context of eye disorders, there is also ranibizumab, which was first approved in 2006 for nAMD, DME, and macular edema following retinal vein occlusion (RVO), and Eylea™ (aflibercept), authorized in 2011 for nMAD. In clinical trials, the main measure of which was a change in Best-Corrected Visual Acuity (BCVA), brolucizumab outperformed aflibercept in minor endpoints and was non-inferior in primary endpoints, and it showed a higher remission of retinal thickness when compared to ranibizumab [68].

Table 4. Biologic for eye disorders approved by the Food and Drug Administration in 2022.

Trade Name and Active Ingredient	Class	Target/Mechanism of Action	Original Approval Date	Manufacturer	Therapeutic Indication
Vabysmo™ (faricimab) [2][18]	Bispecific mAb	VEGF-A and Ang-2	28 January 2022	Genentech, Inc.	nAMD and DME

nAMD—Neovascular (Wet) Age-Related Macular Degeneration; DME—Diabetic Macular Edema; VEGF—Vascular Endothelial Growth Factor; Ang-2—Angiopoietin-2.

In contrast to brolucizumab, faricimab is a bispecifc humanized antibody [2][18]. The small size of the immunoglobulin fragments mechanism found in brolucizumab and its drug delivery features are important characteristics for Biologics, and these are also seen as important characteristics in bispecific mAbs, such as faricimab, whose mechanism is to inhibit two pathways, enhancing the fight against many diseases. Faricimab exerts anti-vascular endothelial growth factor-A (VEGF-A) and anti- angiopoietin-2 (Ang-2) activity [69]. In clinical trials, faricimab demonstrated similar outcomes in the same measure (BCVA) and anatomic improvement when compared to brolucizumab. However, further research is required [70].

Ongoing Clinical Trials for Faricimab

Regarding the potential of faricimab to treat other conditions, in this year (2023), a phase 2 trial has begun for faricimab to test non-proliferative diabetic retinopathy, but no results have been posted yet [71]. This year, two phase 3 trials are expected to be completed to test faricimab in macular edema due to hemiretinal vein occlusion, retinal vein occlusion, and central retinal vein occlusion [72][73]; no results have been posted yet for those studies as well.

5. Enzymes and Proteins

Three out of the fifteen Biologics to get the green light in 2022 fall into the class of proteins and enzymes, as found in **Table 5**.

Table 5. Proteins and enzymes approved by the Food and Drug Administration in 2022.

Trade Name and Active Ingredient	Class	Target/Mechanism of Action	Original Approval Date	Manufacturer	Therapeutic Indication
Xenpozyme™ (olipudase alfa) [1] [2][74][75]	Enzyme	ASM replacement therapy, reducing SM accumulation	31 August 2022	Genzyme Corporation	ASMD
Rolvedon™ (eflapegrastim) [2][76]	rhG-CSF combined with an FC Fragment of human IgG4	Binds to G-CSF receptors	9 September 2022	Spectrum Pharmaceuticals, Inc.	Decrease the incidence of infection, as manifested by chemotherapy-induced Neutropenia
NexoBrid™ (anacaulase) [1] [77]	Compound of Enzymes	Dissolves burn wound eschars	28 December 2022	MediWound, Ltd.	Schar removal with partial- or full-thickness thermal burns

[1]—Orphan Drug; ASM—Acid Sphingomyelinase; ASMD—Acid Sphingomyelinase Deficiency; SM—Sphingomyelin; rhG-CSF—Recombinant Human Granulocyte Colony-Stimulating Factor; G-CSF—Granulocyte Colony-Stimulating Factor.

Xenpozyme™ (olipudase alfa) was the first enzyme to be approved by the FDA in 2022. It is a replacement therapy indicated to treat a rare disease named acid sphingomyelinase deficiency (ASMD) (also known as Niemann-Pick Disease) [74][75]. The deficiency of acid sphingomyelinase (ASM) leads to the accumulation of sphingomyelin and other lipids, which can cause involvement of the central nervous system (CNS), hepatosplenomegaly, and/or lung impairment. There are two types of ASMD, type A and type B. The former causes hepatosplenomegaly and CNS impairment, while type B leads to hepatosplenomegaly, and liver and lung impairment, and it may not present CNS disruption [78][79]. In clinical trials, olipudase alfa demonstrated improved clinical symptoms, including enhanced platelet counts, a reduction in liver and spleen volume, and a greater lung diffusing capacity, and it also cleared sphingomyelin from tissues [80][81].

Given the difficulty in managing neutropenia in some cancer treatments, Rolvedon™ (eflapegrastim), which has been approved this year, is an important innovation. In this regard, Biologics for chemotherapy-induced neutropenia (CIN) started in 1991 with filgrastim, followed by pegfilgrastim in 2002. However, since then, the industry has struggled to develop a new Biologic other than biosimilars for CIN. Eflapegrastim has the addition of an Fc Fragment of a human IgG4 [76], which extends its half-life and increases its absorption by the bone marrow. In clinical trials, eflapegrastim demonstrated non-inferior efficacy in reducing neutropenia compared to pegfilgrastim at a reduced dose of G-CSF (Granulocyte-Colony Stimulating Factor); 3.6 mg and 6.0 mg, respectively, administered in all four cycles. Furthermore, the safety profiles of these two drugs are similar [82][83][84].

In 2022, nexoBrid™ (anacaulase) was the only Biologic of topical administration approved with a distinct therapeutic indication: eschar removal in adults with full- or partial-thickness thermal burns. However, it still has significant limitations for the treatment of electrical and chemical burns, or burns to the face and genitalia [77]. Schar removal is a procedure that helps to better manage the wound and wound closure, and when eschar removal occurs in the first hours it can reduce bacterial growth and days of hospitalization [85]. Of note, no Biologic for this indication has been approved by the FDA in recent years.

Ongoing Clinical Trials for Eflapegrastim

Spectrum Pharmaceuticals Inc. is testing eflapegrastim for other conditions: pediatric participants with solid tumors or lymphoma and treated with myelosuppressive chemotherapy [86], to compare the effect of eflapegrastim on the duration of neutropenia in patients with early-stage breast cancer [87], but there are still trials to be carried out. No studies were found for anacaulase and olipudase alfa for diseases other than the primary ones described in the Prescribing Information.

References

1. Martins, A.C.; Oshiro, M.Y.; Albericio, F.; de la Torre, B.G.; Pereira, G.J.V.; Gonzaga, R.V. Trends and Perspectives of Biological Drug Approvals by the FDA: A Review from 2015 to 2021. Biomedicines 2022, 10, 2325.
2. U.S. Food & Drug Administration. Novel Drug Approvals for 2022. Available online: https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2022 (accessed on 2 December 2022).
3. U.S. Food & Drug Administration. FDA Approves Tebentafusp-Tebn for Unresectable or Metastatic Uveal Melanoma. Available online: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tebentafusp-tebn-unresectable-or-metastatic-uveal-melanoma (accessed on 2 December 2022).
4. Dhillon, S. Tebentafusp: First Approval. Drugs 2022, 82, 703–710.
5. Tawbi, H.A.; Schadendorf, D.; Lipson, E.J.; Ascierto, P.A.; Matamala, L.; Castillo Gutiérrez, E.; Rutkowski, P.; Gogas, H.J.; Lao, C.D.; de Menezes, J.J.; et al. Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma. N. Engl. J. Med. 2022, 386, 24–34.
6. U.S. Food & Drug Administration. FDA Approves Tremelimumab in Combination with Durvalumab and Platinum-Based Chemotherapy for Metastatic Non-Small Cell Lung Cancer. Available online: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tremelimumab-combination-durvalumab-and-platinum-based-chemotherapy-metastatic-non (accessed on 2 December 2022).

7. U.S. Food and Drug Administration. IMJUDO® (Tremelimumab-Actl) Injection, for Intravenous Use Initial U.S. Approval: 2022. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761289lbl.pdf (accessed on 8 January 2023).
8. Kang, C. Teclistamab: First Approval. Drugs 2022, 82, 1613–1619.
9. U.S. Food and Drug Administration. ELAHERETM (Mirvetuximab Soravtansine-Gynx) Injection, for Intravenous Use Initial U.S. Approval: 2022. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761310s000lbl.pdf (accessed on 10 January 2023).
10. U.S. Food and Drug Administration. LUNSUMIOTM (Mosunetuzumab-Axgb) Injection, for Intravenous Use Initial U.S. Approval: 2022. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761263s000lbl.pdf (accessed on 23 January 2023).
11. U.S. Food and Drug Administration. FDA Grants Accelerated Approval to Mosunetuzumab-Axgb for Relapsed or Refractory Follicular Lymphoma. Available online: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-mosunetuzumab-axgb-relapsed-or-refractory-follicular-lymphoma (accessed on 8 May 2023).
12. Twomey, J.D.; Zhang, B. Cancer Immunotherapy Update: FDA-Approved Checkpoint Inhibitors and Companion Diagnostics. AAPS J. 2021, 23, 39.
13. Nathan, P.; Hassel, J.C.; Rutkowski, P.; Baurain, J.-F.; Butler, M.O.; Schlaak, M.; Sullivan, R.J.; Ochsenreither, S.; Dummer, R.; Kirkwood, J.M.; et al. Overall Survival Benefit with Tebentafusp in Metastatic Uveal Melanoma. N. Engl. J. Med. 2021, 385, 1196–1206.
14. de la Torre, B.G.; Albericio, F. The Pharmaceutical Industry in 2022: An Analysis of FDA Drug Approvals from the Perspective of Molecules. Molecules 2023, 28, 1038.
15. Fanale, M.A.; Younes, A. Monoclonal Antibodies in the Treatment of Non-Hodgkin's Lymphoma. Drugs 2007, 67, 333–350.
16. Scott, L.J.; Kim, E.S. Emicizumab-Kxwh: First Global Approval. Drugs 2018, 78, 269–274.
17. Syed, Y.Y. Amivantamab: First Approval. Drugs 2021, 81, 1349–1353.
18. Chaplin, S. Faricimab for Treating Wet AMD and Diabetic Macular Oedema. Prescriber 2022, 33, 27–28.
19. Kudo, M. Durvalumab plus Tremelimumab in Unresectable Hepatocellular Carcinoma. Hepatobiliary Surg. Nutr. 2022, 11, 592–596.

20. Moreau, P.; Garfall, A.L.; van de Donk, N.W.C.J.; Nahi, H.; San-Miguel, J.F.; Oriol, A.; Nooka, A.K.; Martin, T.; Rosinol, L.; Chari, A.; et al. Teclistamab in Relapsed or Refractory Multiple Myeloma. N. Engl. J. Med. 2022, 387, 495–505.
21. Janssen Research & Development, LLC. A Study of Teclistamab in Participants with Relapsed or Refractory Multiple Myeloma (MajesTEC-1). Available online: https://clinicaltrials.gov/ct2/show/NCT04557098 (accessed on 9 January 2023).
22. Janssen Research & Development, LLC. Dose Escalation Study of Teclistamab, a Humanized BCMA*CD3 Bispecific Antibody, in Participants with Relapsed or Refractory Multiple Myeloma (MajesTEC-1). Available online: https://clinicaltrials.gov/ct2/show/NCT03145181 (accessed on 9 January 2023).
23. U.S. Food and Drug Administration. FDA Grants Accelerated Approval to Mirvetuximab Soravtansine-Gynx for FRα Positive, Platinum-Resistant Epithelial Ovarian, Fallopian Tube, or Peritoneal Cancer. Available online: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-mirvetuximab-soravtansine-gynx-fra-positive-platinum-resistant (accessed on 10 January 2023).
24. ImmunoGen, Inc. A Study of Mirvetuximab Soravtansine in Platinum-Resistant, Advanced High-Grade Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancers with High Folate Receptor-Alpha Expression (SORAYA). Available online: https://clinicaltrials.gov/ct2/show/NCT04296890?term=NCT04296890&draw=2&rank=1 (accessed on 10 January 2023).
25. Immunocore Ltd. Phase 1b/2 Study of the Combination of IMCgp100 with Durvalumab and/or Tremelimumab in Advanced Cutaneous Melanoma. Available online: https://clinicaltrials.gov/ct2/show/NCT02535078?term=tebentafusp&draw=2&rank=4 (accessed on 26 April 2023).
26. Jonsson Comprehensive Cancer Center. Nivolumab and Relatlimab in Treating Participants with Advanced Chordoma. Available online: https://clinicaltrials.gov/ct2/show/NCT03623854?term=nivolumab+and+relatlimab&draw=2&rank=4 (accessed on 26 April 2023).
27. Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. Study of Nivolumab and Relatlimab in Patients with Microsatellite Stable (MSS) Advanced Colorectal Cancer. Available online: https://clinicaltrials.gov/ct2/show/NCT03642067?term=nivolumab+and+relatlimab&draw=2&rank=5 (accessed on 26 April 2023).
28. Bristol-Myers Squibb. A Study of Nivolumab and Relatlimab in Combination with Bevacizumab in Advanced Liver Cancer (RELATIVITY-106). Available online: https://clinicaltrials.gov/ct2/show/NCT05337137?term=nivolumab+and+relatlimab&draw=2&rank=7 (accessed on 26 April 2023).

29. Jose Lutzky, M.D. Nivolumab Plus Relatlimab in Patients with Metastatic Uveal Melanoma. Available online: https://clinicaltrials.gov/ct2/show/NCT04552223?term=nivolumab+and+relatlimab&draw=2&rank=8 (accessed on 26 April 2023).
30. Peter Black, P.U. Trial of Local Cystoscopic Injection of Tremelimumab Plus Systemic Durvalumab for High Risk Non-Muscle Invasive Bladder Cancer (Rideau). Available online: https://clinicaltrials.gov/ct2/show/NCT05120622?term=tremelimumab&draw=2&rank=1 (accessed on 28 April 2023).
31. AstraZeneca Durvalumab and Tremelimumab for Pediatric Malignancies. Available online: https://clinicaltrials.gov/ct2/show/NCT03837899?term=tremelimumab&draw=2&rank=2 (accessed on 28 April 2023).
32. Stephen Hodi, F. Phase I Clinical Trial of Tremelimumab Plus MEDI3617 in Patients with Unresectable Stage III or Stage IV Melanoma. Available online: https://clinicaltrials.gov/ct2/show/NCT02141542?term=tremelimumab&draw=2&rank=7 (accessed on 28 April 2023).
33. M.D. Anderson Cancer Center. Mirvetuximab Soravtansine as First Line in Treating Patients with Triple Negative Breast Cancer. Available online: https://clinicaltrials.gov/ct2/show/NCT03106077?term=mirvetuximab+soravtansine&draw=2&rank=4 (accessed on 29 April 2023).
34. Konstantinopoulos, P.; Dana-Farber Cancer Institute. A Phase 2 Study of Mirvetuximab Soravtansine (IMGN853) and Pembrolizumab in Endometrial Cancer (EC). Available online: https://clinicaltrials.gov/ct2/show/NCT03835819?term=Mirvetuximab+Soravtansine&draw=2&rank=9 (accessed on 29 April 2023).
35. Lazaros Lekakis, A.P. CAR-T Cell Therapy, Mosunetuzumab and Polatuzumab for Treatment of Refractory/Relapsed Aggressive Non-Hodgkin’s Lymphoma (NHL). Available online: https://clinicaltrials.gov/ct2/show/NCT05260957 (accessed on 29 April 2023).
36. Washington University School of Medicine. Mosunetuzumab Consolidation Therapy after AutoSCT in r/r Aggressive B Cell Lymphoma. Available online: https://clinicaltrials.gov/ct2/show/NCT05412290?term=mosunetuzumab&draw=2&rank=1 (accessed on 29 April 2023).
37. Roche, H.-L. A Study Evaluating the Safety, Efficacy, and Pharmacokinetics of Mosunetuzumab in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia. Available online: https://clinicaltrials.gov/ct2/show/NCT05091424 (accessed on 29 April 2023).
38. Roche, H.-L. A Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Subcutaneously Administered Mosunetuzumab to Participants with Systemic Lupus Erythematosus. Available online: https://clinicaltrials.gov/ct2/show/NCT05155345?term=mosunetuzumab&draw=2&rank=5 (accessed on 29 April 2023).

39. Dhillon, S. Sutimlimab: First Approval. Drugs 2022, 82, 817–823.
40. Hirsch, J.S. FDA Approves Teplizumab: A Milestone in Type 1 Diabetes. Lancet Diabetes Endocrinol. 2022, 11, 18.
41. U.S. Food and Drug Administration. TZIELDTM (Teplizumab-Mzwv) Injection, for Intravenous Use Initial U.S. Approval: 2022. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761183s000lbl.pdf (accessed on 10 January 2023).
42. U.S. Food and Drug Administration. BRIUMVITM (Ublituximab-Xiiy) Injection, for Intravenous Use Initial U.S. Approval: 2022. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761238s000lbl.pdf (accessed on 9 January 2023).
43. Gooderham, M.J.; van Voorhees, A.S.; Lebwohl, M.G. An Update on Generalized Pustular Psoriasis. Expert Rev. Clin. Immunol. 2019, 15, 907–919.
44. Bachelez, H.; Choon, S.-E.; Marrakchi, S.; Burden, A.D.; Tsai, T.-F.; Morita, A.; Turki, H.; Hall, D.B.; Shear, M.; Baum, P.; et al. Inhibition of the Interleukin-36 Pathway for the Treatment of Generalized Pustular Psoriasis. N. Engl. J. Med. 2019, 380, 981–983.
45. Ingelheim, B. BI655130 Single Dose in Generalized Pustular Psoriasis. Available online: https://clinicaltrials.gov/ct2/show/NCT02978690 (accessed on 3 January 2023).
46. U.S. Food and Drug Administration. OCREVUSTM (Ocrelizumab) Injection, for Intravenous Use Initial U.S. Approval: 2017. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761053lbl.pdf (accessed on 9 January 2023).
47. Steinman, L.; Fox, E.; Hartung, H.-P.; Alvarez, E.; Qian, P.; Wray, S.; Robertson, D.; Huang, D.; Selmaj, K.; Wynn, D.; et al. Ublituximab versus Teriflunomide in Relapsing Multiple Sclerosis. N. Engl. J. Med. 2022, 387, 704–714.
48. U.S. Food and Drug Administration. FDA Approves First Drug That Can Delay Onset of Type 1 Diabetes. Available online: https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-can-delay-onset-type-1-diabetes (accessed on 10 January 2023).
49. U.S. Food and Drug Administration. ENJAYMOTM (Sutimlimab-Jome) Injection, for Intravenous Use Initial U.S. Approval: 2022. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761164s000lbl.pdf (accessed on 10 January 2023).
50. U.S. Food and Drug Administration. FDA Approves Treatment for Adults with Rare Type of Anemia. Available online: https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-treatment-adults-rare-type-anemia (accessed on 10 January 2023).

51. Röth, A.; Barcellini, W.; D'Sa, S.; Miyakawa, Y.; Broome, C.M.; Michel, M.; Kuter, D.J.; Jilma, B.; Tvedt, T.H.A.; Fruebis, J.; et al. Sutimlimab in Cold Agglutinin Disease. N. Engl. J. Med. 2021, 384, 1323–1334.
52. Mrowietz, U.; Burden, A.D.; Pinter, A.; Reich, K.; Schäkel, K.; Baum, P.; Datsenko, Y.; Deng, H.; Padula, S.J.; Thoma, C.; et al. Spesolimab, an Anti-Interleukin-36 Receptor Antibody, in Patients with Palmoplantar Pustulosis: Results of a Phase IIa, Multicenter, Double-Blind, Randomized, Placebo-Controlled Pilot Study. Dermatol. Ther. 2021, 11, 571–585.
53. Ingelheim, B. A Study to Test How Effective and Safe Different Doses of BI 655130 Are in Patients with a Moderate to Severe Form of the Skin Disease Palmoplantar Pustulosis. Available online: https://beta.clinicaltrials.gov/study/NCT04015518?distance=50&term=spesolimab&rank=1 (accessed on 28 April 2023).
54. Ingelheim, B. A Study Investigating Long-Term Treatment with Spesolimab in People with a Skin Disease Called Hidradenitis Suppurativa Who Completed a Previous Clinical Trial. Available online: https://beta.clinicaltrials.gov/study/NCT04876391?distance=50&term=spesolimab&rank=6 (accessed on 28 April 2023).
55. Ingelheim, B. BI655130 (SPESOLIMAB) Induction Treatment in Patients with Moderate-to-Severe Ulcerative Colitis. Available online: https://clinicaltrials.gov/ct2/show/study/NCT03482635?term=spesolimab&draw=3&rank=13 (accessed on 28 April 2023).
56. Ingelheim, B. A Study to Test Whether Spesolimab Helps People with Crohn's Disease Who Have Symptoms of Bowel Obstruction. Available online: https://clinicaltrials.gov/ct2/show/NCT05013385?term=spesolimab&draw=2&rank=5 (accessed on 28 April 2023).
57. Ingelheim, B. A Study in Patients with Atopic Eczema to Test How Effective BI 655130 Is and How Well It Is Tolerated. Available online: https://clinicaltrials.gov/ct2/show/NCT03822832?term=spesolimab&draw=4&rank=21 (accessed on 28 April 2023).
58. Iznardo, H.; Puig, L. IL-1 Family Cytokines in Inflammatory Dermatoses: Pathogenetic Role and Potential Therapeutic Implications. Int. J. Mol. Sci. 2022, 23, 9479.
59. Weill Medical College of Cornell University. Umbralisib Plus Ublituximab (U2) in Progressive CLL After Novel Therapy. Available online: https://clinicaltrials.gov/ct2/show/NCT04149821?term=ublituximab&recrs=ab&draw=2&rank=2 (accessed on 29 April 2023).
60. City of Hope Medical Center. Tazemetostat in Combination with Umbralisib and Ublituximab for the Treatment Relapsed or Refractory Follicular Lymphoma. Available online: https://clinicaltrials.gov/ct2/show/NCT05152459?term=ublituximab&recrs=ab&draw=2&rank=3 (accessed on 29 April 2023).

61. Bertucci, V.; Solish, N.; Kaufman-Janette, J.; Yoelin, S.; Shamban, A.; Schlessinger, J.; Snyder, D.; Gallagher, C.; Liu, Y.; Shears, G.; et al. DaxibotulinumtoxinA for Injection Has a Prolonged Duration of Response in the Treatment of Glabellar Lines: Pooled Data from Two Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Studies (SAKURA 1 and SAKURA 2). J. Am. Acad. Dermatol. 2020, 82, 838–845.
62. Bertucci, V.; Humphrey, S.; Carruthers, J.; Solish, N.; Muhn, C.; Swift, A.; Rubio, R.G.; Shears, G.; Rosen, N. Comparing Injectable DaxibotulinumtoxinA and OnabotulinumtoxinA in Moderate and Severe Glabellar Lines: Additional Analyses From a Phase 2, Randomized, Dose-Ranging, Double-Blind, Multicenter Study. Dermatol. Surg. 2017, 43, S262–S273.
63. Solish, N.; Carruthers, J.; Kaufman, J.; Rubio, R.G.; Gross, T.M.; Gallagher, C.J. Overview of DaxibotulinumtoxinA for Injection: A Novel Formulation of Botulinum Toxin Type A. Drugs 2021, 81, 2091–2101.
64. U.S. Food and Drug Administration. DAXXIFYTM (DaxibotulinumtoxinA-Lanm) for Injection, for Intramuscular Use Initial U.S. Approval: 2022. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761127s000lbl.pdf (accessed on 23 January 2023).
65. Revance Therapeutics, Inc. Efficacy and Safety of Botulinum Toxin Type A for Injection to Treat Glabellar Lines. Available online: https://www.clinicaltrials.gov/ct2/show/NCT02303002?term=NCT02303002&draw=2&rank=1 (accessed on 4 January 2023).
66. Brundridge, W.L.; Czyz, C.N.; Foster, J.A.; DeBacker, C.M.; Holck, D.E.E. Comparison of Prabotulinumtoxin A to Onabotulinumtoxin A in the Treatment of Lateral Canthal Rhytids: A Side-by-Side, Randomized, Double-Blind Comparison. Am. J. Cosmet. Surg. 2021, 38, 259–266.
67. Markham, A. Brolucizumab: First Approval. Drugs 2019, 79, 1997–2000.
68. Finger, R.P.; Dennis, N.; Freitas, R.; Quenéchdu, A.; Clemens, A.; Karcher, H.; Souied, E.H. Comparative Efficacy of Brolucizumab in the Treatment of Neovascular Age-Related Macular Degeneration: A Systematic Literature Review and Network Meta-Analysis. Adv. Ther. 2022, 39, 3425–3448.
69. Shirley, M. Faricimab: First Approval. Drugs 2022, 82, 825–830.
70. Khanani, A.M.; Patel, S.S.; Ferrone, P.J.; Osborne, A.; Sahni, J.; Grzeschik, S.; Basu, K.; Ehrlich, J.S.; Haskova, Z.; Dugel, P.U. Efficacy of Every Four Monthly and Quarterly Dosing of Faricimab vs Ranibizumab in Neovascular Age-Related Macular Degeneration. JAMA Ophthalmol. 2020, 138, 964.
71. Greater Houston Retina Research. Safety and Efficacy of Faricimab in Patients with NPDR (MAGIC). Available online: https://clinicaltrials.gov/ct2/show/NCT05681884?term=faricimab&draw=2&rank=4 (accessed on 26 April 2023).

72. Roche, H.-L. A Study to Evaluate the Efficacy and Safety of Faricimab in Participants with Macular Edema Secondary to Branch Retinal Vein Occlusion (BALATON). Available online: https://clinicaltrials.gov/ct2/show/NCT04740905?term=faricimab&draw=4&rank=7 (accessed on 26 April 2023).
73. Roche, H.-L. A Study to Evaluate the Efficacy and Safety of Faricimab in Participants with Macular Edema Secondary to Central Retinal or Hemiretinal Vein Occlusion (COMINO). Available online: https://clinicaltrials.gov/ct2/show/NCT04740931?term=faricimab&draw=2&rank=8 (accessed on 26 April 2023).
74. Keam, S.J. Olipudase Alfa: First Approval. Drugs 2022, 82, 941–947.
75. U.S. Food & Drug Administration. FDA Approves First Treatment for Acid Sphingomyelinase Deficiency, a Rare Genetic Disease. Available online: https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-acid-sphingomyelinase-deficiency-rare-genetic-disease (accessed on 2 December 2022).
76. U.S. Food and Drug Administration. ROLVEDONTM (Eflapegrastim-Xnst) Injection, for Subcutaneous Use Initial U.S. Approval: 2022. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761148Orig1s000Corrected_lbl.pdf (accessed on 5 January 2023).
77. U.S. Food and Drug Administration. NEXOBRID® (Anacaulase-Bcdb) for Topical Gel Initial U.S. Approval: 2022. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761192s000lbl.pdf (accessed on 9 January 2023).
78. Pinto, C.; Sousa, D.; Ghilas, V.; Dardis, A.; Scarpa, M.; Macedo, M. Acid Sphingomyelinase Deficiency: A Clinical and Immunological Perspective. Int. J. Mol. Sci. 2021, 22, 12870.
79. Wasserstein, M.P.; Desnick, R.J.; Schuchman, E.H.; Hossain, S.; Wallenstein, S.; Lamm, C.; McGovern, M.M. The Natural History of Type B Niemann-Pick Disease: Results From a 10-Year Longitudinal Study. Pediatrics 2004, 114, e672–e677.
80. Genzyme, a Sanofi Company. Efficacy, Safety, Pharmacodynamic, and Pharmacokinetics Study of Olipudase Alfa in Patients with Acid Sphingomyelinase Deficiency (ASCEND). Available online: https://clinicaltrials.gov/ct2/show/results/NCT02004691?term=olipudase+alfa&draw=2&rank=4 (accessed on 2 January 2023).
81. Wasserstein, M.; Lachmann, R.; Hollak, C.; Arash-Kaps, L.; Barbato, A.; Gallagher, R.C.; Giugliani, R.; Guelbert, N.B.; Ikezoe, T.; Lidove, O.; et al. A Randomized, Placebo-Controlled Clinical Trial Evaluating Olipudase Alfa Enzyme Replacement Therapy for Chronic Acid Sphingomyelinase Deficiency (ASMD) in Adults: One-Year Results. Genet. Med. 2022, 24, 1425–1436.

82. Spectrum Pharmaceuticals Inc. SPI-2012 vs. Pegfilgrastim in Management of Neutropenia in Breast Cancer Participants with Docetaxel and Cyclophosphamide. Available online: https://clinicaltrials.gov/ct2/show/NCT02953340?term=NCT02953340&draw=2&rank=1 (accessed on 5 January 2023).
83. Spectrum Pharmaceuticals Inc. SPI-2012 vs. Pegfilgrastim in the Management of Neutropenia in Participants with Breast Cancer with Docetaxel and Cyclophosphamide (ADVANCE) (ADVANCE). Available online: https://clinicaltrials.gov/ct2/show/NCT02643420?term=NCT02643420&draw=2&rank=1 (accessed on 5 January 2023).
84. Cobb, P.W.; Moon, Y.W.; Mezei, K.; Láng, I.; Bhat, G.; Chawla, S.; Hasal, S.J.; Schwartzberg, L.S. A Comparison of Eflapegrastim to Pegfilgrastim in the Management of Chemotherapy-induced Neutropenia in Patients with Early-stage Breast Cancer Undergoing Cytotoxic Chemotherapy (RECOVER): A Phase 3 Study. Cancer Med. 2020, 9, 6234–6243.
85. Hirche, C.; Citterio, A.; Hoeksema, H.; Koller, J.; Lehner, M.; Martinez, J.R.; Monstrey, S.; Murray, A.; Plock, J.A.; Sander, F.; et al. Eschar Removal by Bromelain Based Enzymatic Debridement (Nexobrid®) in Burns: An European Consensus. Burns 2017, 43, 1640–1653.
86. Spectrum Pharmaceuticals Inc. A Study to Evaluate the Safety and Pharmacokinetics of Eflapegrastim in Pediatric Participants with Solid Tumors or Lymphomas and Treated with Myelosuppressive Chemotherapy. Available online: https://clinicaltrials.gov/ct2/show/NCT04570423?term=eflapegrastim&draw=2&rank=1 (accessed on 28 April 2023).
87. Spectrum Pharmaceuticals Inc. Open-Label, Phase 1 Study to Evaluate Duration of Severe Neutropenia after Same-Day Dosing of Eflapegrastim in Patients with Breast-Cancer. Available online: https://clinicaltrials.gov/ct2/show/NCT04187898?term=eflapegrastim&draw=2&rank=2 (accessed on 28 April 2023).