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BioCentury

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Product Discovery & Development

TransCelerate up to speed

BioCentury This Week

Cover Story

TransCelerate Up to Speed — The precompetitive biopharma consortium has hit key milestones on its initiatives to increase the speed and quality of clinical trials, enable head-to-head studies and improve comparability of data.

Strategy

MedImmune's Warheads — AstraZeneca's latest duo of deals, with Spirogen and ADC Therapeutics, gives the pharma's MedImmune unit all the tools it needs to build out in the antibody-drug conjugate space./A6

Emerging Company Profile

Special Sauce in AMD — Hemera is designing its MAC-based gene therapy to treat dry and wet AMD more safely than other therapies targeting the complement pathway in ocular diseases./A8

Lugworms vs. Superbugs — Adenium is developing antimicrobial peptides with a novel mechanism of action and low resistance potential to replace a decades-old toxic drug for nosocomial multidrug-resistant Gram-negative infections./A9

Regulation

Limiting Amyloid Access — A decision by CMS to limit reimbursement of beta amyloid imaging tools to patients in clinical trials approved by the agency means full coverage is years away./A10

Finance

Ebb & Flow — IPO turkey trot. immatics tops up. Alex Denner's Astex consolation prize. Biodesy cashes in on conformations. Also: Amarin; Ariad; Vanda; Coronado; Anacor; Portola; Receptos; Tekmira; XenoPort, et al./A12

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BioCentury 100™ Indicators

Week ended 10/18/13

PRICES	VOLUME
4322.17	1164.1M shrs
up 3%	up 2%

By Tim Fulmer
Senior Writer

In its first year, the industry's precompetitive experiment **TransCelerate BioPharma Inc.** has hit key milestones in all five of its initial projects aimed at improving the speed and quality of clinical trials. The biopharma consortium also has increased its membership to 18 companies from 10, and could announce its next set of projects this year.

TransCelerate was founded last year after a group of pharma R&D heads concluded that precompetitive collaboration was best way to solve clinical trial bottlenecks. The hope was that the resulting efficiencies would speed up drug development and lower costs for all members.

So far, TransCelerate has launched a network to facilitate member company access to comparator drugs for clinical trials, which should ensure rapid availability of high-quality drugs for head-to-head studies.

The consortium also has designed and is preparing to launch an online portal that will allow companies and clinical trial investigators to exchange trial data and protocols through a single platform, po-

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Roadmaps in Boston

KOLs from academia, biotech, pharma and the investment community are just days away from convening in Boston to create roadmaps for four transformational areas of innovation.

Register online for the SciBX Summit on Innovation in Drug Discovery & Development. Details follow A22.

Luminaries in NorCal

Join BayBio at the 2013 Pantheon Ceremony to honor achievement and excellence in Northern California's life sciences industry. Details follow A22.

Amsterdam Awaits

BioCentury invites applications and nominations to present at the 15th Annual Bio€quity Europe conference. Details on A13.

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tentially speeding up investigator and site selection.

TransCelerate has also published white papers and guidelines on trial and data standards, most of which are available to members and non-members alike via the consortium's website *(see Featured Links, A22)*.

A white paper on standards for risk-based monitoring (RBM) of clinical trials should help companies direct resources to the prospective identification and mitigation of risks to patient safety and data quality, while promoting centralized monitoring of the most important parts of a given trial in place of cumbersome comprehensive on-site visits.

The remaining initiatives on the consortium's initial list include clinical trial site qualification and good clinical practice (GCP) training, and clinical trial data standards. The group has published minimum criteria for GCP training of clinical site investigators and staff, and has published standards for collecting and sharing efficacy data from asthma trials.

"A major advance by itself is just the fact that the pharmas taking part in TransCelerate successfully worked together in the first place," CEO Dalvir Gill told BioCentury.

"We've shown that we're not getting bogged down in excessive bureaucracy and instead have created a functioning infrastructure like any working company. On top of that, we've generated concrete outputs for all of our initiatives," he said.

TransCelerate hasn't said what it wants to tackle next, or whether its projects will get more challenging. When it was founded in August 2012, the members prioritized projects they considered most amenable to short-term fixes *(see BioCentury, Oct. 1, 2012)*.

Networking

In August, TransCelerate announced it had reached a key milestone by setting up a network for obtaining comparator drugs and co-therapies for use in clinical trials and completing the first deal under the network. The network allows participating member companies to purchase approved drugs directly from each other for clinical trials, ensuring an adequate and timely supply.

> ***"We've shown that we're not getting bogged down in excessive bureaucracy and instead have created a functioning infrastructure like any working company."***
>
> **Dalvir Gill, TransCelerate**

Terry Walsh, head of the comparator network initiative at TransCelerate and head of comparator strategy and planning at **GlaxoSmithKline plc**, told BioCentury it was rare for companies to get comparator drugs directly from each other except under one-off agreements.

Instead, he said, companies frequently turn to wholesalers and third-party distributors to purchase the needed drugs on the open market. According to TransCelerate, this practice is inefficient, leads to uncertainty about obtaining the necessary quantity of drugs and can result in supply interruptions.

In July, several members of TransCelerate signed a master service agreement that commits them to offer each other a secure and rapid supply of drugs for clinical trials. Walsh declined to say which companies had signed the agreement.

Cutting out wholesalers could save cost and time, Walsh said, "and we should get a better idea of how those savings materialize moving forward."

However, reducing costs was never the driving objective. "Ensuring quality product for trials has been the main goal," he said.

"Companies in the network cannot cherry-pick drugs to exclude from the agreement," Walsh noted. "If you're a member of the network, your entire portfolio of marketed drugs is made available to other member companies for use as comparators in their clinical trials."

The network ensures that drugs come with stability and regulatory data that promote correct storage and handling processes, reducing waste. It also provides detailed demand data to the supplying company, which can help improve supply chain planning and avoid shortages.

Discussions are ongoing about widening the scope of the agreement to include compounds that are still in development, Walsh said.

Milestones for 2014 include standardizing methods for bulk commercial supply of drugs directly from companies in the network rather than supply based on small allotments in bottles and vials, as well as developing methods for the manufacture and supply of placebos.

Through the portal

Another major milestone during TransCelerate's first year was the design of a single online platform that will allow companies and investigators to share data and documents associated with clinical trials. The fully tested first release of the platform will go live next year.

A cross-industry portal will make it easier for companies and investigators to deliver content and services to one another than if they dealt with one another through their individual sites, Jacalyn Kent of **Eli Lilly and Co.** told BioCentury.

Kent is director of clinical development information and optimization at Lilly.

The initiative originally focused on developing a simple log-on interface for each investigator and company, but has expanded to include regulators and to allow all three stakeholder groups to share clinical trial data and protocols.

"What was initially envisioned as simply a common computer interface or log-on portal for drug companies and clinical trial investigators has, over the course of the year, transitioned into less of a portal and into more of an overarching IT platform for TransCelerate companies, investigators and regulators to exchange a variety of clinical trial data," Kent said.

The platform creates a one-stop shop for information on investigators and companies instead of requiring them to use multiple systems to get the same information.

For companies, centralizing information on investigators — such as qualifications, relevant experience and contact

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This Week in *SciBX*

Revving up cGAS — UT Southwestern researchers have confirmed the role of cyclic GMP-AMP signaling in the innate immune system, making a case for developing adjuvants that agonize the pathway or antagonists of the pathway to treat autoimmune conditions. SciBX Table of Contents, A4.

TransCelerate's progress report

About a year after its founding, the not-for-profit pharma consortium **TransCelerate Biopharma Inc.** has not only reached the first-year milestones it set for its five clinical trial initiatives, it also has additional milestones in place for 2014 and 2015. Over the same period, TransCelerate has expanded from 10 pharma members to 18. Darker shading below denotes milestones that have been met.

Initiatives	Milestones	2012	2013	2014	2015
Standards for risk-based monitoring of clinical trials (RBM)	Publish white paper describing RBM methodology		June		
	Start and run first pilot studies of RBM methodology		2013		
	Start additional pilot studies			2014	
Standards for clinical site qualification and training (SQT)	Standardize good clinical practices (GCP) training protocols		June		
	Design and implement investigator curriculum vitae (CV) template		June		
	Design and implement clinical site profile questionnaire form		June		
	Design and implement additional forms and training guidance			2014	
Standards for clinical efficacy data	Publish standards for first disease area - asthma		Sept		
	Select metadata repository for standards		June		
	Put repository online			1Q14	
	Publish standards for other disease areas			2014	
Common investigator and company site portal	Design version 1 of platform/portal		2013		
	Select software and hardware vendors for platform			1Q14	
	Release version 1 of platform			2014	
	Release subsequent versions of platform				2015
Comparator drug network	Master service agreement (MSA) signed by TransCelerate members		Aug		
	Bulk commercial supply of drugs			2014	
	Manufacture placebo versions of comparator drugs			2014	

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information — will speed up the process of identifying appropriate investigators and staff for trials, said Kent.

Investigators will be able to access an "integrated to-do list" that tracks all of their current activity in any trials being run by member companies.

The platform has common file exchange capabilities for regulatory documents, GCP training modules and other electronic publications.

Firewalls allow companies to control what data are made accessible to whom.

"Now that we've designed it, we're in the process of selecting a vendor for the software interface of the portal as well as a place where we can physically house it. After we make those selections by the first quarter of next year, we will then release the portal at an undisclosed time later in 2014," said Kent.

She said TransCelerate also expects to release updated versions of the platform in 2015.

Risk-based monitoring

The risk-based monitoring (RBM) initiative hit its two main milestones. One was to publish a white paper on an RBM methodology; the other was starting the first pilot study of the methodology.

The RBM approach should enable sponsors to focus resources on activities that will have the greatest impact on patient safety and data integrity in clinical trials.

FDA regulations require sponsors to monitor the conduct of clinical trials to ensure patient safety and data integrity. According to the agency, monitoring includes communicating with the clinical investigator and study site staff; reviewing site processes, procedures and records; and verifying the accuracy of data submitted to the sponsor.

The regulations do not specify how sponsors should accomplish this.

According to a survey conducted by FDA's Clinical Trials Transformation Initiative (CTTI), the predominant method for companies running "major efficacy" trials has been on-site visits conducted every four to eight weeks to evaluate study conduct and review data for each enrolled subject.

According to the survey, non-industry sponsors such as academic centers and government agencies typically monitor trial sites less frequently.

If patient safety and/or data integrity issues are identified during on-site visits, the monitor may propose ways to address the risks while the trial is ongoing.

Instead of relying on comprehensive on-site visits, risk-based monitoring focuses on sites, processes and data elements that are most crucial to a given study or that present the greatest risks to patient safety or data integrity.

The concept is not new. ICH guidelines published in 1996 and 2011 advise sponsors to consider the objective, design, complexity, size, and endpoints of a trial to determine the extent and nature of monitoring that is necessary.

In August, FDA released guidance that said risk-based approaches "are more likely than routine visits to all clinical sites and 100% data verification to ensure subject protection and overall study quality."

The guidance notes that some aspects of monitoring may be adequately or even better served by centralized, or remote, monitoring procedures enabled by technologies such as electronic data capture and electronic records.

"We expect that the pharmaceutical and device industries will, for the foreseeable future, continue to use some amount of on-site monitoring, but we anticipate decreased use of on-site monitoring with evolving monitoring methods and technological

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SciBX This Week

ANALYSIS

COVER STORY

Revving up cGAS
University of Texas Southwestern Medical Center researchers have confirmed the role of cyclic GMP-AMP signaling in the innate immune system, making a case for developing adjuvants that agonize the pathway or antagonists of the pathway to treat autoimmune conditions.

TRANSLATIONAL NOTES

Clinical takeoff for new epigenetic targets
Next year is expected to be a banner year for next-generation epigenetics companies, with key clinical data expected for next-generation drugs and first-generation candidates. Big biotech and pharma companies that carved up the space in recent years might have clinical data even sooner.

TARGETS & MECHANISMS

HER2's outside help
An international team has found that neurokinin 1 substance P receptor, a known player in nausea, pain and inflammation, enhances HER2 signaling in breast cancer. The findings argue for combining antagonists against both receptors to treat cancer.

sFGFR for achondroplasia
French researchers have designed a decoy version of fibroblast growth factor receptor 3 that increased bone length and decreased achondroplasia-associated complications in mice compared with vehicle. The molecule has a longer half-life than other clinical dwarfism candidates focused on correcting abnormal signaling by the receptor.

THE DISTILLERY

This week in therapeutics
Protecting against visceral Leishmaniasis with an HbR-based vaccine; improving smoking cessation with a sazetidine A derivative; treating retinopathy with ANG1; and more…

This week in techniques
In vitro generation of branched polyketides using bacterial polyketide synthase; MMP2-activated, chemotherapeutic nanocarriers for targeted drug delivery; 2-aminoadipic acid as a predictive marker for type 2 diabetes; and more…

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capabilities," the guidance said.

While FDA's guidance describes principles for risk-based monitoring, the TransCelerate position paper provides more detailed recommendations for creating and implementing a risk-based monitoring plan, such as recommending tools and methods for identifying, analyzing and monitoring risks, including determining what triggers should result in increased monitoring activity.

TransCelerate's RBM methodology recommends targeting on-site monitoring to activities that cannot be assessed remotely.

After TransCelerate published its RBM approach, "we then began testing that methodology in pilot studies of clinical trial protocols," said initiative lead Rehbar Tayyabkhan.

Tayyabkhan is executive director of global clinical development at **Bristol-Myers Squibb Co.**

In the pilot, TransCelerate members submitted risk-monitoring plans and protocols for trials to FDA to solicit feedback on how well the RBM approach could identify risks.

So far, nine plans from seven TransCelerate member companies have been submitted to FDA for feedback, Tayyabkhan said.

Additional publications are planned for 2014, including lessons learned from the pilot studies, he said.

Data standards

TransCelerate's clinical data standards initiative aims to identify the most commonly collected data in a specific disease area and develop a universal terminology for describing and categorizing those data in study reports. Doing so should facilitate comparison of clinical data for different products.

In September, TransCelerate published a draft document describing standards for collecting and reporting data from clinical trials in adult asthma.

For each disease included in the initiative, TransCelerate forms a project team consisting of member companies that work in that particular disease. The team then develops standards on how efficacy data are collected, transmitted and shared between companies, CROs, clinicians and regulators.

The standards do not prescribe what data should be collected for a given disease. "It does state that if you collect such-and-such data, these are the agreed upon standards for collecting, reporting and sharing it," said David Jordan, who leads the initiative.

The clinical data standards initiative "addresses the underlying issue of how to compare clinical trial efficacy data across companies and products," he said.

Jordan was divisional VP of statistics and data management at **Abbott Laboratories** and is now a consultant to global pharmaceutical R&D at **AbbVie Inc.**

The asthma draft describes how to categorize and record medical history data in case study reports, how to conduct commonly used tests including peak flow, spirometry and airway responsiveness, and how to record the resulting data.

It also discusses methods for collecting specimens that can be used to measure biomarkers and provides examples for reporting biomarker results in study reports.

The document describes various methods of assessing and recording symptoms and measures of quality of life.

It also describes how to measure and record common adverse events that are of special interest for asthma, such as respiratory

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infections, sinusitis and anaphylaxis.

The asthma user guide was developed under the Coalition for Accelerating Standards and Therapies (CFAST) initiative. CFAST is a collaboration between the **Critical Path Institute** (C-Path) and the **Clinical Data Interchange Standards Consortium** (CDISC), a non-profit organization that is establishing standards to support the acquisition, exchange, submission and archive of clinical research data and metadata.

According to Jordan, TransCelerate will continue to work with CDISC next year to develop similar standards for multiple sclerosis (MS), HCV, as well as cardiovascular endpoint data and QT studies.

Qualification and training

Another milestone for TransCelerate was the standardization in June of GCP training across all of the consortium's member companies under the site qualification and training (SQT) standards initiative.

SQT is intended to eliminate inefficiencies that arise from each drug company asking for the same qualifications and training information from clinical trial sites but asking for it in different ways and formats, Katarina Hugeneck told BioCentury.

"We wanted to figure out a way to simplify that interaction for both clinical trial site personnel and staff as well as for drug companies," added Sue McHale.

Hugeneck and McHale are leads on the initiative. Hugeneck is a consultant in business process, study specific instruction at Lilly. McHale is global project delivery director of R&D/global medicines development at **AstraZeneca plc**.

The GCP training standards allow clinical trial investigators and staff personnel to complete a common training program

> ***"If you're a member of the network, your entire portfolio of marketed drugs is made available to other member companies for use as comparators in their clinical trials."***
>
> **Terry Walsh, TransCelerate and GlaxoSmithKline**

that is recognized by all TransCelerate member companies, making it unnecessary for staff to train and separately qualify for each company's trials.

In addition to standardizing GCP clinical site training, the initiative has created standardized templates for clinical trial investigator CVs and clinical trial site profiles.

Next milestones include developing additional standards for investigator site personnel training, said Hugeneck.

Next steps

Gill said discussions are ongoing within TransCelerate about kicking off new initiatives in 2014. He declined to provide details.

Gill also told BioCentury that TransCelerate is open to adding more members and that the board approved the latest member — **UCB Group**'s UCB Pharma S.A. subsidiary — on Sept. 30.

The 10 founding members are AbbVie, AstraZeneca, **Boehringer Ingelheim GmbH**, BMS, Lilly, GSK, **Johnson & Johnson**, **Pfizer Inc.**, **Roche** and **Sanofi**.

The seven members added over the past year are **Astellas Pharma Inc.**, **Biogen Idec Inc.**, **Braeburn Pharmaceuticals S.p.r.l.**, **Cubist Pharmaceuticals Inc.**, **Merck KGaA**'s EMD Serono Inc. unit, **Forest Laboratories Inc.**'s Forest Research Institute and Onyx Pharmaceuticals Inc.

Onyx was acquired by **Amgen Inc.** last month. Gill told BioCentury he could not yet say whether Amgen might join the consortium or Onyx will drop out as a result of the acquisition.

COMPANIES AND INSTITUTIONS MENTIONED

Abbott Laboratories (NYSE:ABT), Abbott Park, Ill.
AbbVie Inc. (NYSE:ABBV), Chicago, Ill.
Amgen Inc. (NASDAQ:AMGN), Thousand Oaks, Calif.
Astellas Pharma Inc. (Tokyo:4503), Tokyo, Japan
AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.
Biogen Idec Inc. (NASDAQ:BIIB), Weston, Mass.
Boehringer Ingelheim GmbH, Ingelheim, Germany
Braeburn Pharmaceuticals S.p.r.l., Princeton, N.J.
Bristol-Myers Squibb Co. (NYSE:BMY), New York, N.Y.
Clinical Data Interchange Standards Consortium (CDISC), Round Rock, Texas
Critical Path Institute (C-Path), Tucson, Ariz.
Cubist Pharmaceuticals Inc. (NASDAQ:CBST), Lexington, Mass.
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
Forest Laboratories Inc. (NYSE:FRX), New York, N.Y.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Merck KGaA (Xetra:MRK), Darmstadt, Germany
Pfizer Inc. (NYSE:PFE), New York, N.Y.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
Sanofi (Euronext:SAN; NYSE:SNY), Paris, France
TransCelerate BioPharma Inc., Philadelphia, Pa.
UCB Group (Euronext:UCB), Brussels, Belgium

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BioCentury

Strategy

MedImmune's warheads

By Stephen Hansen
Senior Writer

AstraZeneca plc's latest pair of deals — the acquisition of Spirogen Ltd. and a partnership with **ADC Therapeutics S.a.r.l.** — gives the pharma's **MedImmune LLC** biologics unit all the tools it needs for antibody-drug conjugates.

ADCs are one of MedImmune's two primary focus areas in cancer. The other area, immunotherapy, was the driver of MedImmune's acquisition of Amplimmune Inc. for $225 million up front and up to $275 million in milestones.

That deal closed Oct. 7, giving MedImmune a pipeline of cancer immunomodulators, including AMP-514, a mAb against PD-1 receptor (PDCD1; PD-1; CD279) that is in preclinical development for cancer *(see BioCentury, Sept. 9)*.

Eight days later MedImmune announced the two ADC deals.

MedImmune will acquire partner Spirogen for $200 million in cash up front plus up to $240 million in milestones.

The AZ unit also partnered with ADC Therapeutics to co-develop two undisclosed preclinical ADC programs. MedImmune will make a $20 million investment in ADC, which also will receive an undisclosed upfront payment and is eligible for milestones.

ADC Therapeutics has a license to Spirogen's ADC technology under a 2012 deal.

MedImmune is not new to the ADC space, though it has not been as visible as other big biotech and pharma players that have been taking licenses to ADC technologies *(see BioCentury, Aug. 19, & Dec. 20, 2010)*.

MedImmune is developing moxetumomab pasudotox, a legacy program from Cambridge Antibody Technology Group plc, which AstraZeneca acquired in 2006. The molecule is an ADC that consists of a murine anti-CD22 antibody variable fragment fused to PE38, a fragment of Pseudomonas exotoxin A.

Moxetumomab pasudotox moved straight into Phase III testing to treat hairy cell leukemia (HCL) in May after a Phase I trial in 48 patients showed an 88% overall response rate, said Ed Bradley, SVP and head of MedImmune's oncology innovative medicines unit (iMed).

The company, which hopes to submit a BLA in 2017, would not disclose whether it has requested breakthrough designation from **FDA**.

> ***"Spirogen provides a suite of warheads and a wide range of different linkers and conjugation chemistries, so that gives you a great tool kit."***
>
> **Chris Martin, Spirogen**

MedImmune also had a 2005 deal to use ADC technology from **Seattle Genetics Inc.** that was expanded in 2007, but the deal has since been terminated.

According to EVP Bahija Jallal, MedImmune has an undisclosed number of ADC programs in preclinical testing. Details on the technologies used to develop those molecules have not been disclosed.

MedImmune, founded as an antibody discovery and development company, has been developing a site-specific conjugation approach to improve the homogeneity of its ADC products.

The company also has internally developed a toxin warhead and linker technology.

3-way innovation

Jallal said the addition of Spirogen strengthens MedImmune's arsenal of ADC warheads and linker chemistries.

Rather than license the technology, Jallal said MedImmune acquired the company for its integrated approach to the components of an ADC — the antibody, linker and warhead.

It is "important to innovate in all these spaces, and that is not as straightforward to do if you are going to do it just through a license," she said.

As of June 30, MedImmune had disclosed eight mAbs in Phase I or Phase II testing for cancer. Jallal said some could be amenable to development as ADCs.

Spirogen's main assets are its pyrrolobenzodiazepine (PBD) warheads, but the company also has linker and conjuga-

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tion technologies.

"Spirogen provides a suite of warheads and a wide range of different linkers and conjugation chemistries, so that gives you a great tool kit," CEO Chris Martin told BioCentury.

According to Martin, the PBD payloads are two to four times more potent than other cytotoxic agents used in ADCs. The PBDs also have a different mechanism of action in that they cross-link DNA inside the cancer cell.

As a result, the PBDs are not affected by cancer cell resistance machinery. "This means that head-to-head with other toxins, ADCs armed with PBDs tend to be very active," he said.

The potency of PBDs should translate into better efficacy, particularly in resistant tumors or against targets that are expressed at low levels.

While targets like HER2 are highly expressed and internalized, which is ideal for ADCs, others can be more difficult for conventional ADCs because the target antigen may have a low copy count or have a slow rate of internalization.

Spirogen's linkers also give MedImmune flexibility in developing ADCs depending on the target and desired pharmacokinetics, Martin said.

He said Spirogen's linkers either can be cleaved by a specific enzyme or be non-cleavable, in which case the PBD is released via degradation of the mAb.

In addition, Spirogen has developed linkers using undisclosed substrates. Different substrates determine which compartment of the cancer cell the linker is cleaved in and the PBD released.

Martin said the company also has linker technology that effectively turns the PBD warhead into a prodrug. "It inhibits the activity while the linker is in place, but when the linker is inside the cell it releases the potent drug," he said.

Besides ADC Therapeutics, at least four other companies have licensed Spirogen's ADC technology: the **Genentech Inc.** unit of **Roche**, Seattle Genetics, **Ablynx N.V.** and **PolyTherics Ltd.**

Spirogen's existing licensing deals are not part of the acquisition and will be transferred to a holding company 75% owned by private equity firm Auven Therapeutics (formerly Celtic Therapeutics). Both Spirogen and ADC are Auven portfolio companies.

Common cause

Meanwhile, Jallal said the partnership with ADC Therapeutics made sense given that ADC and Spirogen had already been working together. "It made sense for us to align all of our common interests and develop a framework that incorporated both Spirogen and ADC Therapeutics," she said.

Jallal noted that MedImmune and ADC Therapeutics have not yet selected which two of the latter's 10 preclinical programs will be included in the deal. ADC Therapeutics has not disclosed targets or indications for any of its programs.

The two chosen programs will be disclosed after they enter clinical development. ADC Therapeutics has an option to co-promote one of the programs in the U.S.

COMPANIES AND INSTITUTIONS MENTIONED

Ablynx N.V. (Euronext:ABLX), Ghent, Belgium
ADC Therapeutics S.a.r.l., Lausanne, Switzerland
AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.
Genentech Inc., South San Francisco, Calif.
MedImmune LLC, Gaithersburg, Md.
PolyTherics Ltd., London, U.K.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
Seattle Genetics Inc. (NASDAQ:SGEN), Bothell, Wash.
U.S. Food and Drug Administration (FDA), Silver Spring, Md.

Emerging Company Profile

Hemera: Special sauce in AMD

By Tim Fulmer
Senior Writer

Hemera Bioscience Inc. is designing its MAC-based gene therapy to help treat dry and wet age-related macular degeneration more safely than other therapies targeting the complement pathway in ocular diseases. It also may offer more convenient dosing and treat a wider variety of AMD types than marketed injectable VEGF inhibitors.

Both the wet and dry forms of AMD are characterized by over-activation of the complement cascade. While the cascade plays a key role in maintaining the homeostasis of eye supporting tissue and in helping the innate immune system respond to infection, over-activation of the cascade in the retina is associated with chronic pro-inflammatory damage that can lead to blindness.

Given the large number of molecular actors in the complement cascade, the challenge has been identifying a target that can be inhibited to reduce unwanted back-of-the-eye inflammation without impairing the normal function of the cascade.

Hemera's adeno-associated viral (AAV) vector-based gene therapy is designed to inhibit the complement cascade's membrane attack complex (MAC), the most downstream component of the cascade, which directly damages cell membranes. The product delivers the gene encoding the CD59 protein, a naturally occurring inhibitor of MAC.

At least two lines of evidence suggest MAC contributes to AMD pathology and progression, co-founder Rajendra Kumar-Singh told BioCentury.

"First, MAC expression is elevated in about 60-70% patients with dry and wet AMD. Second, in a subpopulation of Japanese people, a genetic polymorphism in one of the components of MAC leads to dysfunction of the complex and higher protection against developing AMD compared with the overall Japanese population," he said. "Those data led us to propose that delivering an inhibitor of MAC directly to the eye could help treat dry and wet AMD."

Kumar-Singh is associate professor of ophthalmology at the **Tufts University School of Medicine**.

Hemera Biosciences Inc.

Boston, Mass.

Technology: Gene therapy targeting the complement pathway

Disease focus: Ophthalmic

Clinical status: Preclinical

Founded: 2010 by Rajendra Kumar-Singh, Jay Duker, Adam Rogers, Elias Reichel

University collaborators: Tufts University

Corporate partners: None

Number of employees: Undisclosed

Funds raised: $3.8 million

Investors: Fireman Capital Partners; undisclosed other investors

CEO: None

Patents: 1 issued in the U.S. and EU covering the use of MAC-based gene therapy to treat ophthalmic diseases

Hemera developed a gene therapy that delivers the gene encoding a soluble recombinant form of human CD59 via intravitreal injection.

The company chose the gene therapy approach at the outset "because we wanted a therapy that you could deliver once and still have long-lasting effects, as opposed to a small molecule or antibody that would presumably require multiple injections to treat this chronic condition," said Kumar-Singh.

In 2011, Kumar-Singh and colleagues published in *PLoS One* that both subretinal and intravitreal delivery of the gene therapy protected mouse models of laser-induced wet AMD.

Kumar-Singh said the MAC-based gene therapy could have advantages over anti-VEGF antibodies as well as compounds targeting the complement pathway.

He noted patients receiving anti-VEGF biologics typically require regular injections that can lead to discomfort and inflammation.

The two biologics approved for AMD are Lucentis ranibizumab from **Roche**'s **Genentech Inc.** unit and **Novartis AG** and Eylea aflibercept from **Regeneron Pharmaceuticals Inc.** and **Bayer AG**.

In addition, because the VEGF inhibitors target only excess blood vessel growth, they are effective only against wet AMD. In contrast, by hitting a mechanism upstream of blood vessel growth, the MAC-based gene therapy could be effective against both the dry and wet forms of the disease, said Kumar-Singh.

Hemera's gene therapy also could have advantages over other products hitting the complement cascade.

At least five companies have antibodies or small molecules in development that target the complement cascade to treat AMD, three of which are in Phase II testing. All hit components sitting upstream of MAC, including complement 3 (C3), complement 5 (C5), complement factor D (CFD) and complement factor H (CFH).

The potential advantage of hitting MAC over those upstream targets is that it could be safer, said Kumar-Singh. "You're going after only the most downstream damaging component of the cascade and thus leaving the rest of the cascade intact to play its normal role in the immune system and tissue homeostasis," he said.

In March, Hemera raised $3.8 million from Fireman Capital Partners and undisclosed investors.

The company is conducting toxicology studies. Kumar-Singh declined to disclose details on a clinical development timeline.

COMPANIES AND INSTITUTIONS MENTIONED

Bayer AG (Xetra:BAYN), Leverkusen, Germany
Genentech Inc., South San Francisco, Calif.
Hemera Biosciences Inc., Boston, Mass.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Regeneron Pharmaceuticals Inc. (NASDAQ:REGN), Tarrytown, N.Y.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
Tufts University School of Medicine, Boston, Mass.

Emerging Company Profile

Adenium: Lugworms vs. superbugs

By Emily Cukier-Meisner
Senior Writer

Adenium Biotech ApS is developing derivatives of arenicin-3 to create a safer antibiotic than colistin to treat infections caused by multidrug-resistant Gram-negative pathogens.

Colistin is a broad-spectrum Gram-negative antibacterial first introduced in 1952. It was replaced by safer antibacterials in the 1970s due to its nephrotoxicity and neurotoxicity, yet it saw a resurgence in the late 1990s as the last line of defense against multidrug-resistant Gram-negative pathogens.

Arenicin-3 originally was identified at **Novozymes A/S** from a screen of more than 500 organisms that looked for novel antimicrobial peptides with broad Gram-negative activity. It is found in the marine lugworm *Arenicola marina*.

Because arenicin-3 binds promiscuously to human proteins, Novozymes generated variant libraries and screened them for reduced protein binding and equal or better activity against Gram-negative pathogens.

Novozymes spun out Adenium in 2011 to develop the resulting hits, while the parent company focused on bioethanol.

"Every generation we introduce a new antibiotic, with enough exposure to enough population, the bacteria will 'crack the code' and become resistant. So what is very important is not only that we develop new antibiotics, but that they have a clear, novel mode of action," said CEO Peter Nordkild.

"We have the same efficacy or better than colistin, but we don't have the side effects, and there's no cross-resistance between bacteria that are resistant to colistin," he said.

Both colistin and arenicins initially associate with the negatively charged outer membrane of Gram-negative bacteria. Colistin then induces cell death by permeabilizing the membrane through mechanisms that are not well understood, but requires a component called "Lipid A" for entry.

In contrast, arenicins disrupt both the outer and inner bacterial membranes without relying on the presence of a particular receptor.

Arenicins also may interfere with bacterial protein synthesis, although Nordkild said it is not yet known whether that mechanism occurs if membrane disruption is blocked.

Arenicins also may be less susceptible to resistance than other antibiotic targets. Nordkild said unpublished data show Adenium's AA139 and AA230 have a spontaneous frequency of resistance for select isolates of *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Acinetobacter baumannii* that is five to six orders of magnitude less than penicillin.

Across panels containing 55-120 multidrug-resistant strains for each of those bacteria, AA230 inhibited 90% of the species in each panel at concentrations of 0.5-4 µg/mL. AA139 did so at 1-8 µg/mL, and colistin at 0.25-8 µg/mL.

Arenicins also have demonstrated better activity than colistin in at least one animal model. In mice with pneumonia, aerosolized AA139 or AA230 reduced bacterial load after 48 hours by more than 10^4, compared to a $10^{1.75}$ reduction for colistin dosed equally by weight. Nordkild said a load reduction of at least 10^3 defines a bactericidal rather than bacteriostatic agent.

Nordkild said arenicins have a wide therapeutic window, as the half-maximal effective dose (ED50) and no observed adverse effect level in mice and minipigs differ by a factor of 25-150.

Nordkild said histamine release is the most likely side effect and should be manageable in a hospital setting.

This month Adenium selected AA139 as the clinical candidate because it had a more favorable pharmacokinetic profile than AA230. The company plans to submit a U.S. IND in 4Q14.

Adenium will develop the peptide in an IV formulation to treat urinary tract infections (UTIs) and an aerosol nebulized formulation for hospital-acquired and ventilator-acquired pneumonia.

Nordkild said UTIs and HAP/VAP are the two largest indications in which the multidrug resistant Gram-negative bacteria specified by the Generating Antibiotics Incentives Now (GAIN) Act predominate.

GAIN gives additional market exclusivity and Priority Review to qualified infectious disease products (QIDPs), including those that target pathogens specified by **FDA**. In July the agency published draft guidance on how to streamline clinical trials of pathogen-focused antibacterials, as required by GAIN (see *BioCentury, Nov. 19, 2012*).

Nordkild said the company is funded through the IND submission, and plans to tap current and two new investors for a $20 million series A round in 1Q14 to last through a Phase II proof-of-concept trial.

Adenium hopes to license the compound or be acquired by Phase II completion in 2Q17.

Novozymes does not hold any rights to Adenium's IP or programs, nor does it hold equity in the company.

Adenium Biotech ApS

Copenhagen, Denmark
Technology: Peptides based on arenicin to treat Gram-negative bacterial infections
Disease focus: Infectious
Clinical status: Preclinical
Founded: 2011 by Peter Nordkild
University collaborators: None
Corporate partners: None
Number of employees: 2
Funds raised: $9.5 million
Investors: Novo Seeds, Sunstone Capital
CEO: Peter Nordkild
Patents: 2 issued covering composition of matter and use of arenicin-3 variants

COMPANIES AND INSTITUTIONS MENTIONED

Adenium Biotech ApS, Copenhagen, Denmark
Novozymes A/S (CSE:NZYM B), Bagsvaerd, Denmark
U.S. Food and Drug Administration (FDA), Silver Spring, Md.

Regulation

Limiting amyloid access

By Erin McCallister
Senior Editor

A decision by the **Centers for Medicare & Medicaid Services** to require coverage with evidence development for beta amyloid imaging agents means that Medicare patients will probably have to wait at least a few more years to receive **Eli Lilly and Co.**'s marketed Amyvid florbetapir outside a clinical trial.

On Sept. 27, CMS issued a final decision to limit reimbursement of beta amyloid imaging to one scan per Medicare patient with dementia or neurodegenerative diseases enrolled in clinical trials under its coverage with evidence development (CED) policy.

CMS said it would cover the technology as long as the patients are enrolled in a clinical trial to develop new AD treatments, preventative agents or prognostic tools; or to resolve "clinically difficult differential diagnoses."

However, the trials must be reviewed and approved by CMS and must evaluate the impact of an **FDA**-approved imaging agent on health outcomes, including survival, the avoidance of futile treatment or tests, or improving or slowing the decline of quality of life.

Qualifying trials also can assess whether there are specific subpopulations, patient characteristics or differential diagnoses that are predictive of improved health outcomes in patients whose management is guided by PET imaging, or if the use of beta amyloid imaging to enrich the enrollment of new compounds for AD leads to improved health outcomes.

Amyvid, an imaging agent labeled with fluorine 18 (F-18) that binds to amyloid plaques, is the only FDA-approved beta amyloid imaging agent.

General Electric Co.'s [18F]-flutemetamol is under review in the U.S. and Europe with an FDA decision expected this year. The PDUFA date is not disclosed.

> ***"The persuasiveness of expert opinion is constrained by the available evidence."***
>
> **Centers for Medicare & Medicaid Services**

Reviewing the evidence

Amyvid was approved in April 2012 to estimate beta amyloid neuritic plaque density in patients with cognitive impairment who are being evaluated for AD and other causes of cognitive decline. Approval was based on the Phase III A07 trial in which Amyvid met the co-primary endpoint of a significant correlation with cortical amyloid burden as measured by histopathology during autopsy ($p<0.0001$).

However, a PET scan using Amyvid is not intended as an absolute diagnosis.

"If a scan is negative, this is consistent with not having Alzheimer's and allows the physician to move on to other diagnoses," said Dan Skovronsky, CEO of Avid Radiopharmaceuticals & VP of Tailored Therapeutics at Lilly.

Following a positive scan, the physician may order additional tests to confirm a diagnosis of AD.

In June 2012, Lilly sent a letter to CMS asking the agency to include beta amyloid PET imaging for cognitive impairment in its national coverage determinations (NCDs) for PET imaging.

CMS started its review of Amyvid in October 2012 and in January held a meeting of its Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) to review the available evidence for beta amyloid imaging.

Because no published data show that PET imaging of beta amyloid in the brain changes health outcomes in patients who display early symptoms of cognitive dysfunction, most panel members voted that there was little evidence to support the use of PET to change patient management *(see BioCentury Feb. 4)*.

CMS issued a preliminary decision in July to limit reimbursement of beta amyloid PET imaging to patients enrolled in clinical trials, and opened a 30-day public comment period.

CMS received 202 comments, with the majority opposed to the agency's preliminary decision to limit access to beta amyloid imaging.

Among the commenters were the **Society of Nuclear Medicine and Molecular Imaging** (SNMMI) and the **Alzheimer's Association**, which published a joint guidance in January on the appropriate use of amyloid PET imaging.

SNMMI said it disagreed with the agency's statement that evidence is not adequate to conclude that PET imaging improves meaningful health outcomes in Medicare beneficiaries who display signs and symptoms of AD.

However, the organization did not cite any supportive data related to the efficacy of beta amyloid imaging on health outcomes or treatment management.

Both SNMMI and the Alzheimer's Association noted that their appropriate use criteria defined the specific subgroups of patients who could benefit from PET imaging.

According to the criteria, amyloid imaging is appropriate for three groups of patients. The first is patients with persistent or progressive unexplained mild cognitive impairment. The second is patients satisfying core clinical criteria for possible AD because of unclear clinical presentation defined as either an atypical clinical course or an etiologically mixed presentation.

The third is patients with progressive dementia and early age of onset (<65 years of age).

The joint guidance also notes that amyloid imaging is inappropriate for patients with core clinical criteria for probable AD with typical age of onset; to determine dementia severity; or when used based solely on a positive family history of dementia or presence of apolipoprotein E (ApoE) epsilon 4.

The guidance also states that amyloid imaging is inappropriate for patients with a cognitive complaint that is unconfirmed on clinical examination; when used in lieu of genotyping for suspected autosomal mutation carriers; in asymptomatic individuals; or for nonmedical use.

Nonetheless, CMS was not swayed.

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"The persuasiveness of expert opinion is constrained by the available evidence," the agency wrote in its final decision memo. "Depending on the evidence, expert opinion may vary from conjectural to conclusive."

The memo added: "Furthermore, we also recognize the expertise of another relevant expert consensus panel that we convened on January 30, 2013 — the MEDCAC."

Four members of the 12-person MEDCAC panel were neurologists.

CMS acknowledged that the clinical trial data published for Amyvid were "promising" to support the exclusion of AD and to enrich clinical trials on the basis of biological factors.

But the agency said "the data are insufficient to conclude that the use of positron emission tomography (PET) amyloid-beta imaging is reasonable and necessary for the diagnosis or treatment" for Medicare beneficiaries with dementia or neurodegenerative disease.

CMS taketh away

Up until the final decision memo, local and regional Medicare carriers could and did reimburse for Amyvid scans on a case-by-case basis.

Now, Skovronsky said, the CMS decision limits local and regional carriers' coverage to clinical trials, which is burdensome.

"Unfortunately the way that CED is designed, you can't start trials until you have agreement with CMS. It's not to say that Lilly doesn't have trials; we do, but they were not designed to answer the specific questions asked by CMS," he said.

In an emailed statement to BioCentury after the final decision, CMS said that ongoing trials of FDA-approved beta amyloid agents "may or may not qualify under the CED policy."

"To make this determination, we would need to see the protocol of the ongoing trial to make sure it addresses the research questions and meets the criteria outlined in our CED final decision memo," the agency added.

Lilly has Phase II and Phase III trials of Amyvid that Medicare beneficiaries could enroll in, but because they were not approved by CMS and do not measure the endpoints included in the CED, new patients would not receive reimbursement for the test.

Additionally, Lilly is running a Phase IV study to determine how Amyvid changes patient management and to evaluate the association between scan status and cognitive decline. The estimated completion date is December 2014.

Once it analyzes those data, Lilly said it may ask CMS to reconsider.

> ***"It's not to say that Lilly doesn't have trials; we do, but they were not designed to answer the specific questions asked by CMS."***
>
> **Daniel Skovronsky, Eli Lilly**

"Depending on the data, it might be possible to reopen the discussion with CMS, but it is too soon to say for sure," Skovronsky told BioCentury.

In the meantime, Lilly believes that the CED places undue burden on patients and limits access.

"Patients will have to go to a clinical trials site, be consented to participate in the trial and this might add burden to the patient simply because they are participating in a trial that might require frequent follow-up visits. A second factor is that it will be limited in terms of where patients can participate and the trial may not be available in all areas," he added.

Lilly wouldn't say just how long it would take before new trials could get started, but "this will be a lot more time," Skovronsky said.

CMS would not comment on the details of any trials that might be submitted under the CED or how long they would need to be. It did say in the final decision memo that they could be "short-term" trials that measure the effect of the imaging agent on treatment management or longer trials with outcome determined by postmortem analysis.

Skovronsky said patient and physician groups like the Alzheimer's Association are working on a plan to address the concerns raised within the CED through a potential registry trial.

"While there are no plans finalized yet, discussions are beginning, and we are really encouraged by the leadership role that Alzheimer's Association is taking. We are eagerly waiting to see how that develops," he said.

"One of the key starting points is to understand where the opportunities are and the best way forward as a community," said Eric Dozier, senior director of the Alzheimer's business division at Lilly.

Skovronsky wouldn't give specifics but said the majority of patients eligible for Amyvid are covered by Medicare. "To a large extent, this is the population that would benefit the most from Amyvid. There are people who have AD or cognitive impairment at earlier ages, but the bulk of patients are covered by Medicare."

Lilly gained Amyvid in its 2010 acquisition of Avid Radiopharmaceuticals Inc. The pharma doesn't break out Amyvid sales.

GE declined BioCentury's request for an interview.

COMPANIES AND INSTITUTIONS MENTIONED

Alzheimer's Association, Chicago, Ill.
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
General Electric Co. (NYSE:GE), Fairfield, Conn.
Society of Nuclear Medicine and Molecular Imaging (SNMMI), Reston, Va.
U.S. Centers for Medicare & Medicaid Services (CMS), Baltimore, Md.
U.S. Food and Drug Administration (FDA), Silver Spring, Md.

Ebb & Flow

Turkey trot

By Michael Flanagan, Stephen Hansen & Samantha McGirr
Staff Writers

Even with the traditional post-Thanksgiving break fast approaching, buysiders say there is still plenty of demand to support companies in the IPO queue. But timing will be increasingly tight for those that haven't filed publicly by the end of this week.

The number of biotechs in the queue grew to 23 last week as three new names were added and one — **ADMA Biologics Inc.** (NASDAQ:ADMA) — slipped out the door. The antibody play raised $28.5 million on the OTC Bulletin Board on Thursday.

Among the dozen buysiders who spoke with BioCentury, the near-unanimous consensus was that demand is still strong as generalist and momentum investors continue to chase returns — even after more than 40 life science IPOs have priced this year.

"It is hard to know how long this window will last, and we all know that at some point it will close. But it has been a great year, and at least for the moment, the aftermarket performances continue to look good," said Joep Muijrers of LSP-Life Sciences Partners.

The interest from generalists can be a double-edged sword, noted Muijrers, as a major blowup could send them all running for the hills. "But so far demand continues to look strong," he said.

One thing that is clear: VCs will make sure there is no shortage of supply as long as there is demand for new biotech paper.

Buysiders unanimously said the pace of "test the waters" meetings with private biotechs has not slackened, suggesting that they — along with the bulge bracket banks underwriting many of the new deals — do not believe the end is nigh.

Indeed, six of the eight new filings over the past two weeks have a bulge bracket bank as the lead underwriter.

They will need to move fast if they want to get the deals done

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Earnings on deck

At least 18 biotechs and pharmas are slated to report earnings this week. **Alexion Pharmaceuticals Inc.** (NASDAQ:ALXN), **Celgene Corp.** (NASDAQ:CELG), **The Medicines Co.** (NASDAQ:MDCO) and **Shire plc** (LSE:SHP; NASDAQ:SHPG) are all expected to report double-digit EPS growth on revenue increases of 10% or more. Revenues for Alexion, which markets Soliris eculizumab for rare blood disorders, are expected to jump 34% to $395.3 million. Celgene's top line is expected to increase 15% to $1.6 billion. Medicines Co., which markets drugs for acute and intensive care settings, is expected to post a 27% increase in revenues to $173.9 million. And revenues for specialty biopharma Shire are expected to climb 11% to $1.2 billion. 3Q13 EPS for **Cubist Pharmaceuticals Inc.** (NASDAQ:CBST) is expected to fall 36% despite a 13% increase in revenues to $268.6 million. In April, the biotech provided 2013 R&D expense guidance of $400-$420 million. Cubist reported $277.7 million in R&D expenses in 2012. Cubist markets the antibiotic Cubicin daptomycin. 3Q13 EPS for **Eli Lilly and Co.** (NYSE:LLY) is expected to increase 30% on a 6% revenue increase. In July, the company completed a $1.5 billion share repurchase program. (A) Fiscal 2Q; (B) Spun out of **Abbott Laboratories** (NYSE:ABT) at the start of 2013

Company	Date	Pre/ post mkt	3Q13 EPS est	3Q12 EPS	Expected chg
Illumina Inc. (NASDAQ:ILMN)	10/21	Post	$0.40	$0.41	-2%
Forest Laboratories Inc. (NYSE:FRX) (A)	10/22	Pre	$0.15	$0.15	0%
Novartis AG (NYSE:NVS; SIX:NOVN)	10/22	Pre	$1.31	$1.34	-2%
Waters Corp. (NYSE:WAT)	10/22	Pre	$1.23	$1.18	4%
Amgen Inc. (NASDAQ:AMGN)	10/22	Post	$1.78	$1.67	7%
Cubist Pharmaceuticals Inc. (NASDAQ:CBST)	10/22	Post	$0.35	$0.55	-36%
Sigma-Aldrich Corp. (NASDAQ:SIAL)	10/22	Post	$1.00	$0.94	6%
Eli Lilly and Co. (NYSE:LLY)	10/23	Pre	$1.03	$0.79	30%
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK)	10/23	Pre	$0.90	$0.85	6%
The Medicines Co. (NASDAQ:MDCO)	10/23	Pre	$0.21	$0.17	24%
Thermo Fisher Scientific Inc. (NYSE:TMO)	10/23	Pre	$1.28	$1.19	8%
Bristol-Myers Squibb Co. (NYSE:BMY)	10/23	Post	$0.44	$0.41	7%
Alexion Pharmaceuticals Inc. (NASDAQ:ALXN)	10/24	Pre	$0.79	$0.60	32%
Celgene Corp. (NASDAQ:CELG)	10/24	Pre	$1.54	$1.29	19%
Shire plc (LSE:SHP; NASDAQ:SHPG)	10/24	Pre	$1.65	$1.36	21%
BioMarin Pharmaceutical Inc. (NASDAQ:BMRN)	10/24	Post	-$0.30	-$0.04	NA
AbbVie Inc. (NYSE:ABBV) (B)	10/25	Pre	$0.78	NA	NA
UCB Group (Euronext:UCB)	10/25	NA	NA	NA	NA

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this year.

"Based on folks we have talked to, nearly every company working on a deal is trying to get it done before Thanksgiving," said Valence Fund's Eric Roberts.

"It is usually tough to get people to make speculative bets after November, but some deals might slip through in December only because it is such a hot market," he added.

> ***"It is usually tough to get people to make speculative bets after November but some deals might slip through in December only because it is such a hot market."***
>
> **Eric Roberts, Valence Fund**

Immunotherapy top up

Cancer vaccine company **immatics biotechnologies GmbH** may have raised its last private financing round, as investors gave it enough cash to submit regulatory applications for lead program IMA901.

Last week, immatics raised €12 million ($16.3 million) in the first tranche of a €34 million ($46.1 million) series D round. CEO Paul Higham told BioCentury the additional cash will finance the company beyond 2015, when final Phase III data are expected for IMA901 in renal cell carcinoma (RCC). The funds will support regulatory submissions in the U.S. and Europe for the vaccine containing tumor-associated peptides (TUMAPs).

If the Phase III data are positive, Higham said immatics would seek a large cancer-focused commercial partner for IMA901. And if all goes to plan, immatics may not require another venture financing, he said.

> ***"The environment for cancer immunotherapy has improved significantly."***
>
> **Paul Higham, immatics**

A 2010 series C round of €53.8 million ($70.5 million) that would have covered the Phase III trial to the interim data readout, which is expected in 1H14. At the time, investors decided immatics would have to go it alone in Phase III because prospective pharma partners viewed cancer immunotherapy as too risky *(see BioCentury, Sept. 27, 2010)*.

"That has really changed," Higham noted. "The environment for cancer immunotherapy has improved significantly. It is really quite different from even 18 months ago, where big pharma were on a much more cautious footing."

He added: "We've seen companies who in the past were saying immunotherapy was too high risk and they weren't interested, those companies are now saying they've made a decision and it is part of their future."

Higham noted much of the interest has come with the success of other immunotherapies that modulate the immune system like IMA901 — such as melanoma drug Yervoy ipilimumab from

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Bristol-Myers Squibb Co. (NYSE:BMY) — and the clinical success of other checkpoint inhibitors like programmed cell death 1 ligand 1 (CD274 molecule; PD-L1; B7-H1).

He said there could be significant synergy between cancer vaccines like IMA901, which promote tumor-directed T cells, and checkpoint inhibitors that prevent immune resistance at the site of the tumor.

"That is the way to go in my view," Higham said.

Existing investors participated in the series D round: dievini Hopp BioTech; Wellington Partners; MIG Funds; AT Impf; Grazia Equity; EMBL Ventures; SB Asset Management; KfW; National Technology Enterprises; Merifin Capital; Beacon Hill; and PB Invest.

Consolation prize

While Alex Denner's campaign to derail **Otsuka Pharmaceutical Co. Ltd.**'s takeout of Astex Pharmaceuticals Inc. fell short, his hedge fund still made $1.1 million on its two-month investment.

Sarissa Capital Management began taking a position in Astex in mid-August, and had purchased 459,387 shares at $5.13-$6.61 by the close of Sept. 3, the day before media reports of a potential bid from Otsuka.

> ***"In the end we made money, so it wasn't a huge deal."***
>
> **Alex Denner, Sarissa**

On Sept. 5, Astex agreed to a cash offer of $8.50 per share, or $866 million, representing a 27% premium to Astex's close on Sept. 3.

Both companies' boards unanimously approved the deal, which was structured as a tender offer. A majority of shareholders needed to tender their shares by Oct. 10 to complete the deal.

Believing Otsuka's offer undervalued Astex, Denner bought 3.9 million shares at $8.49, raising Sarissa's stake to 5%.

He then began lobbying publicly against the deal.

Denner told Bloomberg on Sept. 11 the price was "exceptionally low" based on Astex's pipeline. On Oct. 2 he issued a public letter recommending fellow shareholders not tender their shares.

In the letter, Denner said Astex did not contact all potential bidders and called the timing "inexplicable" given near-term readouts for SGI-110, a second-generation version of cancer drug Dacogen decitabine.

In August, Astex said SGI-110 led to an overall remission rate of 25% in 67 evaluable acute myelogenous leukemia (AML) patients. Additional data are expected in December and next year.

Astex responded with an open letter of its own on Oct. 2, saying "33 pharmaceutical companies were contacted to gauge their interest," but only Otsuka submitted a final proposal.

Last week, Denner told BioCentury his primary goal was to delay the deal to give new bidders more time to emerge.

"A lot of people said they were thinking the same way we were; and we came close. But they got 52%, which was just enough" for the deal to go through, he said. "In the end we made money, so it wasn't a huge deal."

All told, Sarissa paid $36 million for its Astex stake. At the $8.50 takeout price, the firm will receive $37.1 million.

Sarissa's other biotech investment is a 2% stake, as of July 23, in **Vivus Inc.** (NASDAQ:VVUS). Denner sits on the obesity company's board.

The firm also participated in a September $7.5 million private round by hematology company **Emmaus Life Sciences Inc.**

Cashing in on Conformations

Biodesy Inc. has yet to commercialize its system for protein structure analysis, but a trio of investors are betting the platform's low cost and simplicity will eventually allow for scalability and customizability.

Last week, Biodesy raised $15 million in a series A round led by 5AM Ventures. Pfizer Venture Investments and Roche Venture Fund also participated. All are new investors.

Biodesy is developing its second-harmonic generation (SHG) technology, which enables real-time, high throughput measurement of protein conformational changes with subangstrom resolution.

5AM's Andrew Schwab, who joined Biodesy's board, said the VC was drawn to the straightforward technology.

"The key differentiator is that it's a fairly simple and robust assay," he said. "Typical binding assays are not very good at detecting conformational changes. And technology for detecting structural changes is much more laborious and expensive than the SHG technology."

Greg Yap, who was named CEO last week, said the real-time aspect of SHG technology allows researchers to confirm not only whether a compound binds a target protein, but also that it induces the correct conformational change.

Yap was formerly healthcare entrepreneur-in-residence at **General Electric Co.** (NYSE:GE). Prior to that, he oversaw the cancer assay portfolio at Ventana Medical Systems, a unit of **Roche** (SIX:ROG; OTCQX:RHHBY).

> ***"The key differentiator is that it's a fairly simple and robust assay."***
>
> **Andrew Schwab, 5AM Ventures**

The SHG platform has high potential for high throughput screening of allosteric modulators, according to Yap.

"For allosteric modulators, you need an assay that can distinguish between molecules sticking somewhere on a protein and those that cause the proper functional change," he said.

In the near term, Biodesy plans to partner with pharmas and academic institutions to refine the platform and develop its customer base.

According to Yap, Biodesy entered its first partnership with an undisclosed pharma prior to the series A close.

The company's long-term goal is to be a supplier of instruments, reagents and assays.

Yap said Biodesy has not set a timeline for a commercial launch. But he expects the series A to be "more than sufficient" to get the SHG technology to market as well as develop additional applications for specific types of drug discovery.

Schwab said the Biodesy investment came from the $200 million 5AM Ventures III L.P. fund.

In an SEC filing last week, 5AM disclosed plans to raise up to $240 million for its fourth fund. Schwab declined to comment.

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Regulatory milestones

Alimera Science Inc. (NASDAQ:ALIM) fell $0.23 to $2.48 on Friday after FDA issued a complete response letter for an NDA for Iluvien fluocinolone acetonide intravitreal implant to treat diabetic macular edema. Alimera said FDA requested an additional clinical trial plus at least 12 months of follow-up. Alimera has rights to Iluvien from **pSivida Corp.** (NASDAQ:PSDV; ASX:PVA), which lost $0.93 (24%) to $2.87 on Friday. In Australia, the stock was down A$0.52 (12%) to A$3.84.

Alimera said it will meet with FDA's Dermatologic and Ophthalmic Drug Advisory Committee in January for advice. The complete response letter is the third from FDA for Iluvien.

Alimera lost $0.89 (26%) on the week. pSivida fell $1.74 (38%). In Australia, the stock lost A$1.15 (23%).

AMAG Pharmaceuticals Inc. (NASDAQ:AMAG) gained $1.68 to $21.53 last week after FDA extended the PDUFA date by three months for an sNDA for Feraheme ferumoxytol. The new date is Jan. 21; it was Oct. 21. Feraheme is under review to expand its indication to include the treatment of all adult patients with iron deficiency anemia who have failed or could not tolerate oral iron treatment *(see Analyst Picks, A18)*.

The product is approved to treat iron deficiency anemia in adult patients with chronic kidney disease (CKD).

Amarin Corp. plc (NASDAQ:AMRN) fell $3.61 to $2.01 on Thursday after FDA's Endocrinologic and Metabolic Drugs Advisory Committee voted 9-2 against expanding the label of Vascepa icosapent ethyl. Amarin is seeking approval for Vascepa to treat high triglycerides in patients with mixed dyslipidemia in combination with statins. The committee voted against approval prior to the completion of Amarin's REDUCE-IT cardiovascular outcomes trial. Data are not expected until at least 2016 *(see "Analyst Picks," A18)*.

The sNDA has a Dec. 20 PDUFA date. Amarin already markets Vascepa in the U.S. as an adjunct to diet to reduce triglyceride levels in adults with severe hypertriglyceridemia.

Amarin finished the week down $3.06 (60%) to $2.03.

Ariad Pharmaceuticals Inc. (NASDAQ:ARIA) fell $1.83 (41%) to $2.67 on Friday after discontinuing the confirmatory Phase III EPIC trial of Iclusig ponatinib in newly diagnosed leukemia patients due to arterial thrombotic events observed in patients treated with the drug. Earlier this month, FDA placed a partial clinical hold on all trials of Iclusig *(see Analyst Picks, A18)*.

The drug is approved for patients with chronic myelogenous leukemia (CML) or Philadelphia-chromosome positive (Ph+) acute lymphoblastic leukemia (ALL) who are resistant to or intolerant of prior treatment with tyrosine kinase inhibitors (TKIs). Ariad said it expects FDA to narrow the label for Iclusig to patients who have failed other therapies.

Ariad lost $1.59 (37%) on the week.

Ironwood Pharmaceuticals Inc. (NASDAQ:IRWD) was off $0.18 to $10.70 last week after Germany's Federal Joint Committee (G-BA) said in a final benefit assessment that Constella linaclotide has "no additional benefit" over comparators to treat irritable bowel syndrome with constipation (IBS-C). **Almirall S.A.** (Madrid:ALM) has European rights to Constella from Ironwood.

MannKind Corp. (NASDAQ:MNKD) added $0.17 to $5.28 last week after resubmitting an NDA to FDA for Afrezza to improve glycemic control in Type I and II diabetics. The resubmission includes data from two additional trials that were requested by FDA in a 2011 complete response letter, the agency's second for the dry power formulation of insulin plus an inhaler.

Medivation Inc. (NASDAQ:MDVN) was down $0.15 to $50.82 last week after the U.K.'s NICE issued draft guidance recommending use of Xtandi enzalutamide to treat hormone-relapsed, metastatic prostate cancer in men whose disease has progressed on or after docetaxel therapy. The recommendation is contingent on partner **Astellas Pharma Inc.** (Tokyo:4503) providing Xtandi at an undisclosed discount under a patient access scheme. Comments are due Nov. 8.

The European Commission approved Xtandi to treat metastatic castration-resistant prostate cancer (CRPC) in June.

ThromboGenics N.V. (Euronext: THR) was down €0.41 to €18.67 last week after G-BA said in a final benefit assessment that vitreomacular traction (VMT) drug Jetrea ocriplasmin provides "significant" additional benefit vs. watchful waiting in mild disease but "no additional benefit" in severe disease. ThromboGenics and partner **Novartis AG** (NYSE:NVS; SIX:NOVN) will now negotiate a price for Jetrea with Germany's Statutory Health Insurance Funds Association (GKV-Spitzenverband).

UCB Group (Euronext:UCB) rose €1 to €46.76 on Friday after FDA expanded the label of Cimzia certolizumab pegol to include treatment of adults with active ankylosing spondylitis, but issued a complete response letter for active axial spondyloarthritis. UCB had been seeking to expand Cimzia's label to include treatment of active axial spondyloarthritis, including patients with ankylosing spondylitis.

Cimzia is approved in the U.S. for active psoriatic arthritis, rheumatoid arthritis (RA) and Crohn's disease.

UCB gained €1.65 on the week.

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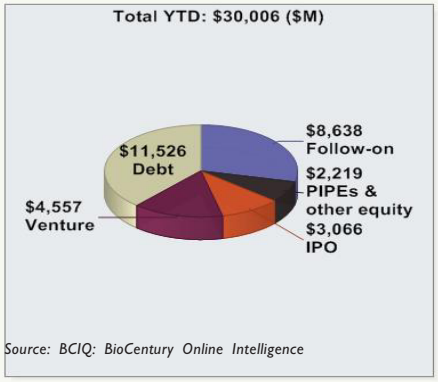
Money Raised in 2013

Last week, the biotech industry raised $286 million, bringing to $30 billion the total raised year-to-date. In 2012, a total of $36.3 billion was raised, including $19.9 billion in debt, $6.3 billion in follow-ons, $2.8 billion in PIPEs and other equity, $1.1 billion in IPOs, and $6.2 billion in venture capital. Totals include overallotments and warrants, and are rounded to the nearest millions.



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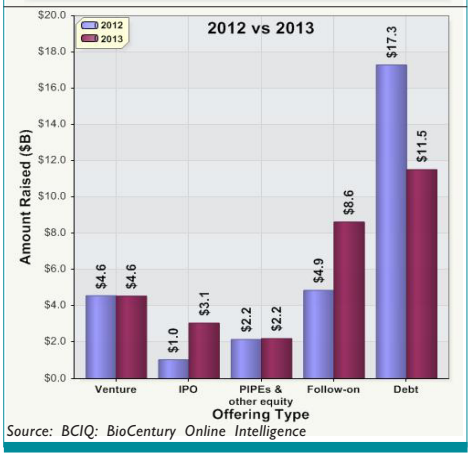

Source: BCIQ: BioCentury Online Intelligence

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Vanda Pharmaceuticals Inc. (NASDAQ:VNDA) lost $1.89 (19%) to $7.83 last week after FDA said a panel will meet on Nov. 14 to discuss an NDA for Vanda's Hetlioz tasimelteon (VEC-162) to treat non-24-hour sleep wake disorder in totally blind patients. The NDA is under Priority Review with a Jan. 31 PDUFA date. Vanda previously said FDA had set a tentative date for a committee to discuss Hetlioz.

Clinical milestones

Coronado Biosciences Inc. (NASAQ:CNDO) fell $3.86 (67%) to $1.91 last Monday after its *Trichuris suis* ova (TSO) missed the primary endpoint in a Phase II TRUST-I trial to treat Crohn's disease *(see B18)*.

Partner **Dr. Falk Pharma GmbH** is evaluating TSO for Crohn's in the Phase II TRUST-II trial, with data expected this quarter. Coronado said it will analyze data from both trials to determine next steps for TSO.

Coronado lost $3.99 (69%) to $1.78 on the week.

Keryx Biopharmaceuticals Inc. (NASDAQ:KERX) closed up $1.73 (20%) to $10.49 on Wednesday on the release of an abstract showing that Zerenex ferric citrate met the primary endpoint in a Phase II trial to treat hyperphosphatemia in non-dialysis dependent patients with chronic kidney disease (CKD). The data are slated to be presented at the American Society of Nephrology meeting in November *(see B20)*.

Earlier this month, FDA accepted for review an NDA for Zerenex to treat hyperphosphatemia in CKD patients on dialysis. Keryx said it expects to receive the PDUFA date in the next few weeks.

Keryx continued to rise to finish the week up $1.92 (21%) to $11.26.

Medivir AB (SSE:MVIR B) was up SEK5.50 to SEK106.50 on Friday after presenting data from an open-label Phase III trial evaluating simeprevir (TMC435) in patients with HCV genotype 1 infection co-infected with HIV-1. Simeprevir plus peginterferon and ribavirin led to a sustained virologic response (SVR) 12 weeks after the end of treatment, the primary endpoint, in 74% of patients *(see B20)*.

Last month, Japan's Ministry of Health, Labor and Welfare (MHLW) approved simeprevir as Sovriad to treat HCV genotype 1 infection. Simeprevir is under Priority Review in the U.S. with an undisclosed PDUFA date; a six-month Priority Review would place the PDUFA date in November.

Johnson & Johnson (NYSE:JNJ) has ex-Nordic rights to develop and commercialize simeprevir from Medivir.

Medivir gained SEK4.75 on the week.

Regeneron Pharmaceuticals Inc. (NASDAQ:REGN) gained $17.22 to $307.65 on Wednesday after it and partner **Sanofi** (Euronext:SAN; NYSE:SNY) said subcutaneous alirocumab (REGN727) met the primary endpoint in the Phase III ODYSSEY MONO trial to treat primary hypercholesterolemia *(see B22)*.

The data are the first from the 12-trial Phase III ODYSSEY program evaluating alirocumab as monotherapy and in combination with other lipid-lowering agents. Data from additional ODYSSEY trials are expected next year.

Regeneron gave back some of its gains to finish the week up $13.26 to $303.56.

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Amgen Inc. (NASDAQ:AMGN), which is developing competitor hyperlipidemia compound AMG 145, gained $4.03 to $114.92 last week. AMG 145 is in Phase III testing, with data expected in 1Q14.

Ebb & Flow

Ablynx N.V. (Euronext:ABLX) was up €0.07 to €7.58 on Friday after granting **Eddingpharm Inc.** exclusive, Chinese rights to develop and commercialize ALX-0141, which is in Phase I testing to treat postmenopausal osteoporosis. Ablynx will receive €2 million ($2.7 million) up front and is eligible for undisclosed milestones, plus tiered double-digit royalties. ALX-0141 is a nanobody against receptor activator of NF-kappa B ligand (RANKL).

Ablynx was up €0.25 on the week.

Look for **Actelion Ltd.** (SIX:ATLN) to move this week. After market close on Friday, FDA approved Opsumit macitentan to treat PAH. Actelion plans to launch Opsumit next month. Last week, Actelion was up CHF1.05 to CHF64.60 after saying it is on track to meet its goal of double-digit core earnings growth in 2013. Sales rose 4% to CHF1.3 billion ($1.5 billion), including a 3% increase in sales of pulmonary arterial hypertension (PAH) drug Tracleer bosentan to CHF1.14 billion ($1.3 billion) *(see EPS Watch, A20)*.

ADMA Biologics Inc. (OTCQB:ADMA) was up $0.03 to $8.53 in its first week of trading after raising $28.5 million in an IPO on the OTC Bulletin Board. ADMA sold 3.4 million shares at $8.50, which values the company at $78.4 million. Last month, ADMA said it planned to sell 2.7 million shares at $8.50-$9.50.

ADMA's RI-002 is in Phase III testing to treat primary immunodeficiency disease, with preliminary data expected in 4Q14 and a BLA submission slated for 1H15. RI-002 is a human plasma-derived, polyclonal IV Ig that has standardized high levels of antibodies against respiratory syncytial virus (RSV).

Immunotherapy company **Advaxis Inc.** (NASDAQ:ADXS) was off $1.95 (34%) to $3.75 in its first week of trading on NASDAQ after raising $23 million through the sale of 5.8 million shares at $4 in a follow-on. The follow-on includes five-year warrants to purchase 2.9 million shares at $5. Advaxis ceased trading on OTCQB. The company subsequently sold the $3.5 million overallotment, bringing the total raised to $26.5 million.

Anacor Pharmaceuticals Inc. (NASDAQ:ANAC) gained $3.06 (28%) to $13.83 on Friday after announcing that an arbitrator awarded the company $100 million in damages in a contract dispute with **Valeant Pharmaceuticals International Inc.** (TSX:VRX; NYSE:VRX). The dispute covers a 2004 deal between Anacor and Dow Pharmaceutical Sciences Inc., under which Dow was providing services to help Anacor develop its topical antifungal agent tavaborole. Valeant — which is developing efinaconazole, a competitor to tavaborole — acquired Dow in 2008 *(see B7)*.

An NDA for tavaborole is under FDA review for onychomycosis, with a July 29, 2014, PDUFA date.

Anacor gained $2.72 (24%) on the week.

Mirati Therapeutics Inc. (NASDAQ:MRTX) added $0.80 to $17.80 last week after saying it plans to sell 3 million shares in a follow-on. Mirati proposed to raise up to $57.5 million in the offering on Oct. 2, when its share price was $18.48. The company's mocetinostat is in Phase II testing for myelodysplastic syndromes (MDS), with a Phase III trial slated for 2H14.

Paladin Labs Inc. (TSX:PLB) was up C$0.67 to C$63.55 on Friday after an FDA panel voted that the company had adequately demonstrated the safety and efficacy of Impavido miltefosine to treat visceral, cutaneous and mucosal leishmaniasis. The company is seeking approval for Impavido for all three forms of the disease. The compound is under Priority Review, with a Dec. 19 PDUFA date.

Paladin acquired Impavido from **Aeterna Zentaris Inc.** (TSX:AEZ; NASDAQ:AEZS) in 2008. Aeterna was off C$0.02 to C$1.48 on Friday, while the stock was off $0.03 to $1.43 on NASDAQ.

Paladin gained C$0.84 on the week. Aeterna lost C$0.03 on the week. On NASDAQ, the stock was off $0.03.

Portola Pharmaceuticals Inc. (NASDAQ:PTLA) added $1.14 to $23.75 last week after raising $105.9 million through the sale of 4.5 million shares at $23.75 in a follow-on. Portola first proposed to raise up to $100 million in the offering last week, when its share price was $26.74. Company shareholders also sold 1.9 million shares at $23.75 in a concurrent secondary offering.

Portola's betrixaban is in Phase III testing for prevention of venous thromboembolism (VTE) in high-risk acutely medically ill patients.

Receptos Inc. (NASDAQ:RCPT) jumped $6.22 (23%) to $33.22 on Wednesday on rumors that **Celgene Corp.** (NASDAQ:CELG) and **Teva Pharmaceutical Industries Ltd.** (NYSE:TEVA) are making bids to acquire Receptos for more than $700 million. Celgene and Teva said they do not comment on rumors. Receptos could not be reached for comment.

Receptos' most advanced product is RPC1063, a selective sphingosine 1-phosphate receptor 1 (S1PR1; S1P1; EDG1) agonist that is in a Phase II/III trial to treat relapsing multiple sclerosis (MS). Data from the Phase II portion are expected in mid-2014. Receptos finished the week up $5.71 (20%) to $33.91.

Celgene was up $7.38 to $160.55 on the week, while Teva lost $1.04 to $40.

Stallergenes S.A. (Euronext:GENP) gained €0.30 to €58.80 and **DBV Technologies** (Euronext:DBV) was up €0.76 (10%) to €8.60 on Friday after partnering to develop and commercialize a birch allergy product using DBV's Viaskin skin patch technology and birch pollen allergen from Stallergenes. Stallergenes will have development and commercialization rights. DBV is eligible for up to €145 million ($196.7 million) in milestones, plus royalties *(see B5)*.

Stallergenes was up €1.33 on the week. DBV rose €0.85 (11%).

Stemline Therapeutics Inc. (NASDAQ:STML) closed off $2.79 to $35.20 on Friday after proposing to raise $90 million in a follow-on. Next year, Stemline plans to start a Phase IIb trial of SL-401 to treat blastic plasmacytoid dendritic cell neoplasm and a Phase III trial in third-line acute myelogenous leukemia (AML). SL-401 is an IL-3 receptor targeting agent.

Stemline lost $2.06 on the week.

RNAi company **Tekmira Pharmaceuticals Corp.** (TSX:TKM; NASDAQ:TKMR) added C$0.48 to C$9.32 and gained $0.47 to $9.01 on NASDAQ on Friday after raising $30 million through the sale of 3.8 million shares at $8 in a follow-on. Tekmira proposed the offering late Wednesday, when its share price on NASDAQ was $8.82.

Tekmira's lead internal candidate is TKM-PKL1, which is in

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Phase I/II testing to treat advanced gastrointestinal neuroendocrine tumors and adrenocortical carcinoma, with data expected in mid-2014. TKM-PLK1 comprises short interfering RNA (siRNA) targeting polo-like kinase 1 (PLK1; STPK13) formulated with the company's lipid nanoparticle (LNP) technology.

Tekmira lost C$0.56 on the week. On NASDAQ, the stock was off $0.65.

XenoPort Inc. (NASDAQ:XNPT) rose $0.27 to $5.89 last week after investor Clinton Group Inc. called for the resignation of XenoPort CEO Ronald Barrett and a shift in the company's focus away from commercializing Horizant gabapentin enacarbil and toward developing XP23829. XP23829 is in Phase I testing for relapsing-remitting multiple sclerosis (RRMS) and in preclinical development for psoriasis.

Clinton said Horizant — approved in the U.S. to treat restless leg syndrome (RLS) and to manage postherpetic neuralgia (PHN) — "will never be the commercial success we all wish it were."

Clinton Group, which has a 2.7% stake in XenoPort, also said the fair value of XenoPort is $13-$16 per share and that the shares are undervalued due to a lack of confidence in the biotech's management.

Corrections

Ariad Pharmaceuticals Inc. (NASDAQ:ARIA), Cambridge, Mass.
Business: Cancer

On Oct. 9, Chairman and CEO Harvey Berger said Ariad's Phase III EPIC trial of Iclusig ponatinib in newly diagnosed CML patients was likely to have been expanded, but the company did not say how many additional patients would have been required.

The Oct. 14 BioCentury misstated Berger's title and mischaracterized the planned expansion of EPIC and the timing of the interim data. On Oct. 18, Ariad discontinued the Phase III EPIC study after updated data from the pivotal Phase II PACE trial showed longer use of Iclusig was associated with increased risk of treatment-emergent serious arterial thrombotic events. The interim analysis is no longer planned.

Separately, an investigator-run Phase II study in 80 newly diagnosed CML patients is testing a 30 mg dose of Iclusig in a cohort of those patients. Data from that trial are expected at the American Society of Hematology (ASH) meeting in December.

The Oct. 14 BioCentury misstated the number of patients receiving the 30 mg dose and when data were expected.

Endocyte Inc. (NASDAQ:ECYT), West Lafayette, Ind.
Business: Cancer

Endocyte reported that a DSMB recommended continuing the vintafolide plus docetaxel and the docetaxel monotherapy arms in the Phase IIb TARGET trial to treat second-line non-small cell lung cancer (NSCLC). The Oct. 14 edition of BioCentury omitted the information.

Analyst picks & changes

Company	Bank	Analyst	Coverage	Opinion	Wk chg	10/118 cls
AMAG Pharmaceuticals Inc. (NASDAQ:AMAG)	Baird	Christopher Raymond	Upgrade	Outperform (from neutral)	8%	$21.53
Raymond also raised his target to $26 from $25 after FDA extended the PDUFA date by three months for an sNDA for anemia drug Feraheme ferumoxytol. He said applications with three-month PDUFA extensions have a "decent" record of gaining FDA approval. The new date is Jan. 21, 2014. The sNDA seeks to expand Feraheme's indication to all adult patients with iron deficiency anemia who have failed or could not tolerate oral iron treatment. Feraheme is approved to treat iron deficiency anemia in adult patients with chronic kidney disease (CKD).						
Amarin Corp. plc	Canaccord	Ritu Baral	Downgrade	Hold (from buy)	-60%	$2.03
(NASDAQ:AMRN)	H.C. Wainwright	Andrew Fein	Downgrade	Neutral (from buy)		
Baral also lowered her target to $3 from $10 after FDA's Endocrinologic and Metabolic Drugs Advisory Committee voted 9-2 against expanding the label of the company's Vascepa icosapent ethyl to adults with high triglycerides with mixed dyslipidemia. Baral estimates a 15% chance of approval by the Dec. 20 PDUFA date. The committee voted against approval prior to the completion of Amarin's REDUCE-IT cardiovascular outcomes trial, which are not expected until at least 2016 *(see B12)*. Amarin markets Vascepa in the U.S. as an adjunct to diet to reduce triglyceride levels in adults with severe hypertriglyceridemia Fein also lowered his target to $2.50 from $10 on the panel vote.						
Ariad Pharmaceuticals Inc. (NASDAQ:ARIA)	JPMorgan	Cory Kasimov	Downgrade	Neutral (from overweight)	-37%	$2.67
Kasimov also removed his $12 target after Ariad discontinued the confirmatory Phase III EPIC trial evaluating Iclusig ponatinib in newly diagnosed chronic myelogenous leukemia (CML) patients based on safety data from the trial *(see B24)*. Earlier this month, FDA placed a partial clinical hold on trials of the compound after data from the pivotal Phase II PACE trial showed longer use of Iclusig was associated with increased risk of treatment-emergent serious arterial thrombotic events. Kasimov said doctors will likely reserve Iclusig for use as salvage therapy in patients with the T3151 variant of BCR-ABL tyrosine kinase. He expects Ariad will have to start another confirmatory trial to satisfy FDA accelerated approval requirements. Iclusig is approved to treat CML and Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) that is resistant or intolerant to prior treatment with tyrosine kinase inhibitors (TKIs).						

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Company	Bank	Analyst	Coverage	Opinion	Wk chg	10/118 cls
Coronado Biosciences Inc.	Canaccord	Salveen Richter	Downgrade	Hold (from buy)	-69%	$1.78
(NASDAQ:CNDO)	MLV	Graig Suvannavejh	Downgrade	Hold (from buy)		
	Roth Capital Partners	Joseph Pantginis	Downgrade	Neutral (from buy)		
	Wedbush	Christopher Marai	Downgrade	Neutral (from outperform)		

Richter also lowered her target to $2 from $18 after Coronado's *Trichuris suis* ova (TSO) missed the primary endpoint in the Phase II TRUST-I trial to treat Crohn's disease *(see B18)*. While Coronado observed activity in patients with severe Crohn's, Richter now "questions" the TSO platform, saying TRUST-1 was critical in validating the approach. TSO comprises ova from *T. suis*, a porcine helminth. The ova act as a natural immunomodulator to regulate T cells and inflammatory cytokines following colonization of the host intestinal tract. TSO is also in investigator-initiated Phase II trials to treat ulcerative colitis, multiple sclerosis (MS), autism and psoriasis, for which data are expected this quarter.

Suvannavejh also lowered his target to $2 from $15 and removed all TSO-related revenue from his model, noting the "relatively limited information" for the platform's potential in severe patients.

Pantginis also lowered his target to $2 from $24 on the TSO results.

Marai also lowered his target to $3 from $13 and now views CNDO-109 as the primary value driver for Coronado. CNDO-109, a cell therapy that activates natural killer (NK) cells, is in Phase I/II testing for acute myelogenous leukemia (AML). Marai expects Coronado to begin Phase IIb testing with CNDO-109 next year.

Exact Sciences Corp. (NASDAQ:EXAS)	Wedbush	Zarak Khurshid	Upgrade	Outperform (from neutral)	12%	$11.26

Khurshid upgraded and maintained his $12 target ahead of an anticipated FDA approval of Cologuard in early 2014 and a national reimbursement coverage decision within 90 days of approval. Cologuard is under parallel review by FDA and the Centers for Medicare & Medicaid Services to screen for colorectal cancer. He estimates $234M in 2016 sales for the non-invasive stool DNA test that uses a multiplexed quantitative Invader assay for the simultaneous detection of methylated and unmethylated sequences in the promoter region of the vimentin (VIM) gene.

Geron Corp. (NASDAQ:GERN)	MLV	George Zavoico	New	Buy	39%	$4.28

Zavoico initiated coverage with a $6.50 target ahead of data from an investigator-sponsored Phase II trial of imetelstat (GRN163L) in myelofibrosis (MF) to be presented at the American Society of Hematology (ASH) meeting in December. He said imetelstat showed "promising signs of durable efficacy" in another Phase II trial for essential thrombocythemia data and expects the MF trial to confirm the product's disease-modifying effect. Zavoico believes imetelstat could become the preferred front-line treatment for MF over Jakafi ruxolitinib from **Incyte Corp.** (NASDAQ:INCY). He estimates $1.6B in 2019 sales of imetelstat, an oligonucleotide that competitively inhibits telomerase activity, in MF.

Vivus Inc. (NASDAQ:VVUS)	Piper Jaffray	Charles Duncan	Downgrade	Neutral (from overweight)	-13%	$9.79

Duncan also lowered his target to $11 from $14, saying competition for Qsymia phentermine/topiramate will become "more onerous." While Duncan remains positive on additional reimbursement and a possible commercial partnership in 2014, he said Vivus has "the yeoman's task" of driving acceptance of the pharmacologic treatment of obesity amongst doctors and payers. Duncan also noted that Vivus management shared an estimated 108,000 Qsymia prescriptions of 3Q13, which fell short of IMS Health's prediction of 120,000.

Waters Corp. (NYSE:WAT)	Mizuho	Peter Lawson	Downgrade	Neutral (from buy)	2%	$106.48

Lawson downgraded, noting that the tool supplier's share price is approaching his target of $110. He said he finds it difficult to increase his target due to weak end-market sentiment based on his pharmaceutical and diagnostic surveys. Lawson said his surveys revealed "near-term choppiness" around the pharmaceutical end-market, which represents about 55% of Water's revenues.

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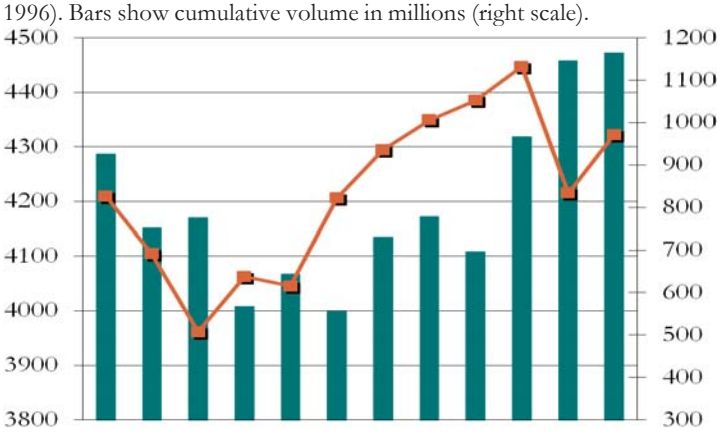
EPS watch

At least six biotechs and pharmas reported earnings last week. Sales of new products helped big pharmas **Johnson & Johnson** (NYSE:JNJ) and **Roche** (SIX:ROG; OTCQX:RHHBY) beat the Street's revenue estimates. For instance, J&J reported a 73% increase in sales of Zytiga abiraterone to $464 million in 3Q13. The drug was approved for metastatic castration-resistant prostate cancer (CRPC) in the U.S. and EU in 2011. The label was expanded to chemotherapy-naïve patients in the U.S. in 2012 and in the EU earlier this year. J&J added $6.1 billion to its market cap last week. In its 3Q13 update, Roche CEO Severin Schwan highlighted uptake of breast cancer drugs Perjeta pertuzumab and Kadcyla ado-trastuzumab emtansine. Perjeta sales in 3Q were CHF78 million ($86 million), while sales of Kadcyla were CHF73 million ($80 million). Perjeta was launched in the U.S. in 2012 and in the EU in March, and Kadcyla was launched in the U.S. in February. Kadcyla uses antibody-drug conjugate technology from **ImmunoGen Inc.** (NASDAQ:IMGN). Roche added $2.8 billion to its market cap last week, while shares of ImmunoGen were up 4% on the week. **Abbott Laboratories** (NYSE:ABT) tacked on more than $5 billion to its valuation after beating the Street's revenue and earnings expectations. The company also increased its quarterly dividend by 57% to $0.22 per share. Molecular diagnostic company **Cepheid Inc.** (NASDAQ:CPHD) closed up 10% on the week after outperforming the Street and raising its 2013 revenue and non-GAAP EPS guidance. Mcap in $M

Company	3Q13 EPS est	3Q13 EPS actual	Outcome	Growth from 3Q12	10/18 cls	Wk chg	% chg	Mcap chg	10/18 Mcap
Abbott Laboratories (NYSE:ABT)	$0.51	$0.55	Beat by $0.04	31%	$37.29	$3.53	10%	$5,471.5	$57,799.5
3Q13 worldwide sales were up 4% to $5.37B. The Street was expecting $5.39B. 3Q13 sales from established pharmaceuticals came in at $1.2B, up 0.6% from 3Q12. Medical device sales were up 4% to $1.3B, while diagnostics sales were up 11% to $1.1B. Sales in emerging markets were $2.2B, up 8%. Percentage changes for sales figures exclude the impact from currency exchange rates. SG&A fell 10% to $1.7B. The pharma spun out its research-based pharmaceutical business **AbbVie Inc.** (NYSE:ABBV) at the start of this year. Abbott reiterated 2013 EPS guidance of $1.98-$2.04.										
Actelion Ltd. (SIX:ATLN)	NA	NA	NA	NA	CHF64.60	CHF1.05	2%	$138.9	$8,547.0
Core EPS for the nine months ended Sept. 30 was CHF3.60, up 21% from CHF3.09 in the same period last year. Total product sales for the first nine months were up 4% to CHF1.3B ($1.5B). Sales of Tracleer bosentan for pulmonary arterial hypertension (PAH) were up 3% to CHF1.1B ($1.3B), while sales of the company's other PAH drug, Ventavis iloprost, fell 2% to CHF83M ($91.3M). Core R&D expenses dropped by 12% to CHF251M ($276M) as a result of last year's cost saving initiative. Actelion reiterated that it expects double-digit core earnings growth in 2013, "at least at the same level" of earnings growth in 2014, and at least single-digit growth in 2015. Percent changes are based on local currencies.										
Baxter International Inc. (NYSE:BAX)	$1.19	$1.19	Met	4%	$66.00	$0.00	0%	$0.0	$35,838.0
3Q13 net sales were up 9% to $3.77B from $3.5B. The Street was expecting $3.81B. Baxter BioScience revenues, which include plasma-based therapies and vaccines, were $1.6B, up 6% from 3Q12. Revenues for the company's Medical Products business, which manufactures products used in the delivery of fluids and drugs to patients, were up 10% to $2.2B. 3Q13 R&D expenses were unchanged at $290M. Baxter expects 3Q13 EPS of $1.24-$1.26.									
Cepheid Inc. (NASDAQ:CPHD)	-$0.12	-$0.02	Beat by $0.10	NA	$40.67	$3.72	10%	$251.4	$2,748.2
The company reported a loss per share of $0.32 in 3Q12. 3Q13 total revenue for the molecular diagnostic company increased 24% to $100.1M from $81M in 3Q12, and beat the Street's estimate of $93.9M. Clinical reagent sales increased 36% to $74.4M. The company raised its 2013 revenue guidance to $389M-$391M from $380-$385M and its non-GAAP EPS guidance to $0.22-$0.24 from $0.18-$0.21.									
Johnson & Johnson (NYSE:JNJ)	$1.32	$1.36	Beat by $0.04	9%	$91.63	$2.18	2%	$6,104.0	$256,564.0
3Q13 sales increased 5% to $17.6B from $17.1B. The Street was expecting $17.4B. Pharmaceutical sales were $7B in 3Q13, up 11% from $6.4B. 3Q13 sales of autoimmune drug Remicade infliximab came in at $1.7B, up 7% from 3Q12. Sales of prostate cancer drug Zytiga abiraterone, which J&J obtained from its 2009 acquisition of Cougar Biotechnology Inc., increased by 73% to $464M. Selling, marketing and administrative expenses increased by 2% to $5.3B in 3Q13. Percentage changes for sales figures exclude the impact from currency exchange rates. The company increased its 2013 guidance for EPS excluding special items to $5.44-$5.49 from $5.40-$5.47.									
Roche (SIX:ROG; OTCQX:RHHBY)	NA	NA	NA	NA	CHF241.10	CHF2.50	1%	$2,833.2	$229,328.6
The pharma did not provide earnings figures for the quarter or the nine months ended Sept. 30. 3Q13 sales grew 8% to CHF11.6B ($12.7B) from CHF11.3B in 3Q12. The Street was expecting CHF11.5B. 3Q13 sales of cancer drug MabThera/Rituxan rituximab rose 12% to CHF1.8B ($2B), while Avastin bevacizumab was up 14% to CHF1.6B ($1.8B) and sales of Herceptin trastuzumab were up 7% to CHF1.5B ($1.7B). The pharma recorded CHF78M ($86M) in worldwide 3Q13 sales of breast cancer drug Perjeta pertuzumab. 3Q13 sales of Kadcyla ado-trastuzumab emtansine were CHF73M ($80M). U.S. sales were up 12% and included a sales reserve release in the third quarter of CHF184M ($202M) related to a provision in the U.S. healthcare reform law. Sales in China were up 23%. The pharma reiterated its expectation that 2013 sales will increase in line with 2012 sales growth. 2012 sales increased 4% to CHF45.5B ($49.7B). All percent changes assume constant currency.									

BioCentury 100 Price & Volume Trend

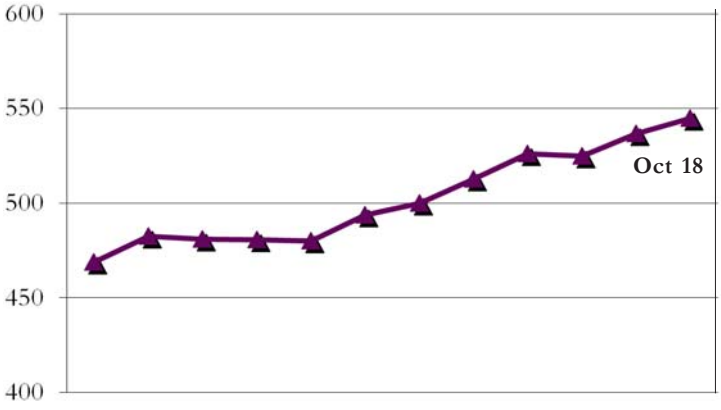
Cumulative weekly performance of 100 bioscience stocks. 12-week period. Line shows Price Level change (Left scale. Index base=1000 on May 10, 1996). Bars show cumulative volume in millions (right scale).



BioCentury tracks 622 issues that report prices and volume daily. The BioCentury 100 is a subset used to monitor price and volume trends.

BioCentury London Index

Weekly change in the combined market capitalization for 14 bioscience stocks listed on the LSE or AIM, 12-week period. Index base =1000 on May 10, 1996.



Price Gains

Stocks with greatest % price increase in the week ended Oct. 18.
(Priced above $2; 5,000 minimum share volume)

Company	Ticker	$Close	$Chg	%Chg	Vol(00)
Geron	GERN	4.280	1.200	39%	361134
Aastrom[1]	ASTM	5.200	1.110	27%	15332
PeptiDream	4587	¥14290	¥3050	27%	51643
Anacor	ANAC	13.830	2.720	24%	34827
GNI Group	2160	¥548	¥100	22%	259040
Keryx	KERX	11.260	1.921	21%	300912
Receptos	RCPT	33.910	5.710	20%	20882
Novogen[2]	NVGN	4.650	0.770	20%	868009
Genfit	ALGFT	€11.310	€1.860	20%	54385
Aratana	PETX	28.040	4.550	19%	11049
Senomyx	SNMX	4.200	0.680	19%	6634
Halozyme	HALO	12.050	1.950	19%	115780
Trovagene	TROV	8.300	1.300	19%	9700

Price Declines

Stocks with greatest % price decline (criteria as above).

Company	Ticker	$Close	$Chg	%Chg	Vol(00)
Amarin[3]	AMRN	2.030	-3.060	-60%	1610385
pSivida[4]	PSDV	2.870	-1.740	-38%	104827
Ariad	ARIA	2.670	-1.590	-37%	1351457
Advaxis	ADXS	3.750	-1.950	-34%	23036
Alimera Sciences	ALIM	2.480	-0.890	-26%	19621
Vanda	VNDA	7.830	-1.885	-19%	41599
Immunomedics	IMMU	4.475	-0.935	-17%	81111
Prosensa	RNA	4.290	-0.800	-16%	19256
Onconova Therap	ONTX	20.680	-3.300	-14%	9657

Volume Gains

Greatest changes in volume above 5,000 shares.

Company	Ticker	Vol(00)	%Chg	$Close	$Chg
Silence Therapeutics	SLN	8743	1873%	255p	-15p
Portola	PTLA	70257	1440%	23.750	1.140
Novogen[2]	NVGN	868009	1335%	4.650	0.770
Advaxis	ADXS	23036	1125%	3.750	-1.950
D. Western	4576	193435	314%	¥1160	-¥179
Sequenom	SQNM	305599	277%	2.420	-0.180
Bind Therapeutics	BIND	8331	245%	15.000	-0.310
Response Bio[5]	RBM	226	224%	C$2.10	-C$0.050
Receptos	RCPT	20882	223%	33.910	5.710

1 Reverse split shares 1-for-20 on 10/16. Price and volume adjusted to reflect split.
2 Includes volume from Australian Stock Exchange with converted ADSs (1ADS = 25 shares)
3 Volume figure is of ADSs (1ADS = 1 share)
4 Includes volume from ASX
5 Includes volume from Toronto Stock Exchange and OTCBB

BioCentury 100 Advance-Decline Trend

Week ended	BC100 Price level	BC100 Stocks gaining	Gaining vol. (00)	BC100 Stocks declining	Declining vol. (00)
Sep 20	4349.18	59	5131580	39	2619537
Sep 27	4385.38	51	3647598	48	3257319
Oct 04	4447.20	52	5397319	46	4233189
Oct 11	4214.86	20	1751917	80	9706436
Oct 18	4322.17	66	5421463	32	6163352

Featured links this week

Links to the following documents reside online on the BioCentury on BioBusiness page of www.biocentury.com.

Biosimilars

Letter from California Gov. Jerry Brown to the California State Senate saying Brown supports allowing biosimilars to be substituted for biologics once FDA has determined they are interchangeable but that the physician notification requirement of a bill that would have allowed substitution of a biosimilar only if FDA declared the biosimilar interchangeable for the specific use is "premature" *(see BioCentury Extra, Monday, Oct. 14)*.

Cancer

Paper published in *The Lancet* on the economic burden of cancer across the EU.

Clinical trials

White paper from **TransCelerate BioPharma Inc.** and **CDISC** on standards for asthma clinical data and guidelines from TransCelerate for site qualification and training *(see Cover Story)*.

HCV

FDA revised draft guidance recommending the use of sustained virologic response (SVR) at 12 weeks after the end of treatment as the primary endpoint in registration trials of chronic HCV therapies *(see BioCentury Extra, Wednesday, Oct. 16)*.

Orphan drugs

Summary of actions taken at the Oct. 8-10 meeting of EMA's Committee for Orphan Medicinal Products (COMP).

Product documentation

— Bosulif: Germany's Federal Joint Committee (G-BA) final benefit assessment concluding that Bosulif bosutinib has an "unquantifiable" additional benefit for adults with chronic, accelerated or blast phase Philadelphia chromosome-positive (Ph+) chronic myelogenous leukemia (CML); from **Pfizer Inc.** (NYSE:PFE) *(see BioCentury Extra, Thursday, Oct. 17)*.

— Constella: Germany's Federal Joint Committee (G-BA) final benefit assessment concluding that Constella linaclotide has "no additional benefit" for irritable bowel syndrome with constipation (IBS-C) vs. a change in diet and symptom-specific treatment, G-BA's requested comparator; from **Almirall S.A.** (Madrid:ALM) and **Ironwood Pharmaceuticals Inc.** (NASDAQ:IRWD) *(see BioCentury Extra, Thursday, Oct. 17)*.

— Giotrif: EMA's CHMP EPAR for Giotrif afatinib to treat locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR mutations in patients who are EGFR tyrosine kinase inhibitor (TKI)-naïve; from **Boehringer Ingelheim GmbH**.

— Impavido: Briefing documents for the Oct. 18 meeting of FDA's Anti-Infective Drugs Advisory Committee, which voted 15-1, 14-2 and 13-3 that the safety and efficacy of Impavido miltefosine to treat visceral, cutaneous and mucosal leishmaniasis, respectively, were adequately demonstrated; from **Paladin Labs Inc.** (TSX:PLB) *(see BioCentury Extra, Friday, Oct. 18)*.

— Incresync: EMA's CHMP EPAR for Incresync alogliptin/pioglitazone to treat Type II diabetics who are uncontrolled on existing therapies; from **Furiex Pharmaceuticals Inc.** (NASDAQ:FURX) and **Takeda Pharmaceutical Co. Ltd.** (Tokyo:4502).

— Jetrea: Germany's Federal Joint Committee (G-BA) final benefit assessment concluding that Jetrea ocriplasmin provides "significant" additional benefit vs. watchful waiting in vitreomacular traction (VMT) patients with mild symptoms, which includes mild to moderate visual impairment; from **ThromboGenics N.V.** (Euronext:THR) *(see BioCentury Extra, Thursday, Oct. 17)*.

— Pixuvri: The U.K.'s NICE draft guidance recommending against Pixuvri pixantrone to treat multiply relapsed or refractory aggressive non-Hodgkin's B cell lymphoma; from **Cell Therapeutics Inc.** (NASDAQ:CTIC; Milan:CTIC).

— Vascepa: Briefing documents for the Oct. 16 meeting of FDA's Endocrinologic and Metabolic Drugs Advisory Committee, which voted 9-2 against expanding the label of Vascepa icosapent ethyl to include treatment of patients with mixed dyslipidemia in combination with statins prior to the completion of Amarin's REDUCE-IT cardiovascular outcomes trial; from **Amarin Corp. plc** (NASDAQ:AMRN) *(see BioCentury Extra, Wednesday, Oct. 16)*.

— Vipidia: EMA's CHMP EPAR for Vipidia alogliptin to treat Type II diabetes in patients who are uncontrolled on existing therapies; from **Furiex Pharmaceuticals Inc.** (NASDAQ:FURX) and **Takeda Pharmaceutical Co. Ltd.** (Tokyo:4502).

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Four Tracks of Innovation

CAR-Based Cellular Therapies

Chimeric antigen receptor (CAR)-based cell therapies made a splash in 2011 when clinical results from three CML patients showed impressive efficacy. Despite their promise, CAR-based approaches still face a host of obstacles on the way to full implementation.

Epigenetics' Second Wind

Emerging novel methyltransferase (HMT) and BET bromodomain targets as well as initial reports on druggable histone demethylases herald a potential second wave of development in the epigenetics space.

New Models in Neurological Diseases

This track will narrow in on the necessary next steps to reinvigorate translational research on schizophrenia, autism and depression.

Non-Coding RNAs as Tools and Targets

The discovery of thousands of non-coding RNAs has contributed to a robust commercial landscape, but fundamental translational issues remain.

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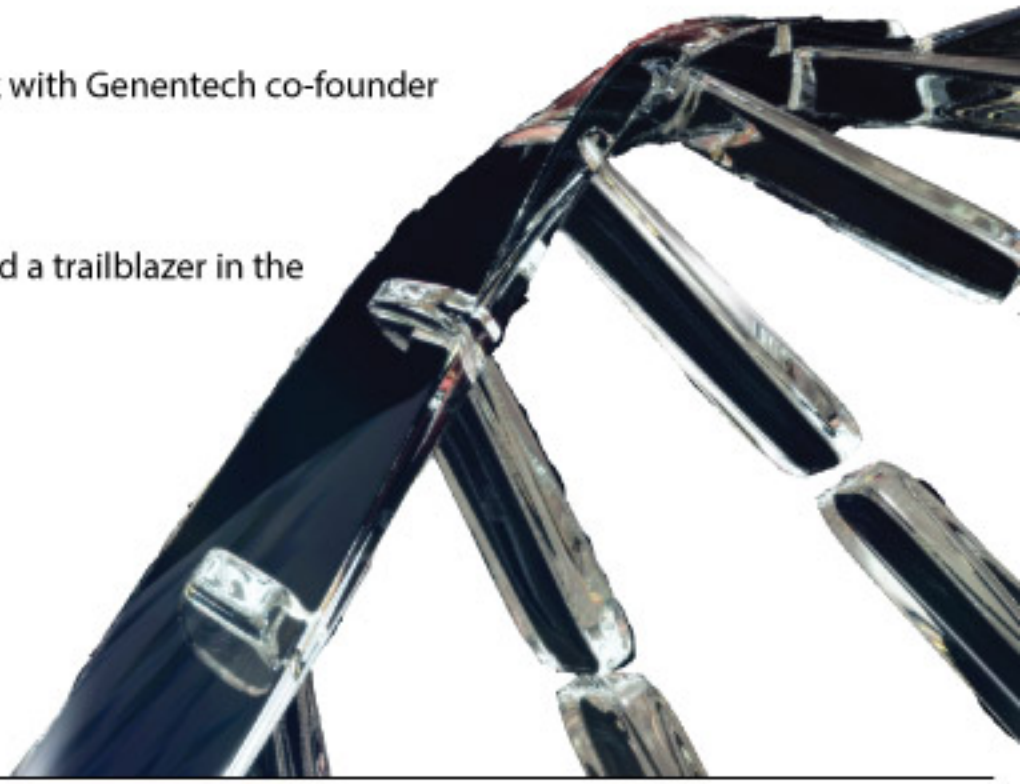

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