**Prix Galien USA Awards 2025**   
Scemblix application

**1) Background information and need for drug/device**

(please be as specific as possible in your description; limit 500 words)

Despite many available treatment options and the common perception that chronic myelogenous leukemia (CML) is the “good cancer,” there remains an urgent need for breakthrough treatments [Hills, 2023]. CML is a rare type of myeloproliferative neoplasm, most commonly defined by the presence of the Philadelphia (Ph) chromosome in approximately 95% of cases [Druker, 2024; Braun, 2020; Manley, 2020]. This chromosomal abnormality results from a reciprocal translocation between chromosomes 9 and 22 [t(9;22)], producing the *BCR::ABL1* fusion oncogene—the key driver of the disease [Braun, 2020].

The first tyrosine kinase inhibitor (TKI) for CML was imatinib (IMA), which was developed and marketed by Novartis as Gleevec and approved by the US FDA in 2001. The impact of this approval was practice-changing and dramatically improved outcomes and survival for CML patients. Prior to Gleevec, the disease was fatal, with a survival of approximately 3-5 years [Druker, 2025]. Gleevec revolutionized CML treatment and came to symbolize a new era of precision medicine, winning multiple Prix Galien Awards including the 2022 Gold Medal in recognition of this achievement [Novartis Press Release, 10/31/2016; The Galien Foundation, 2025].

TKIs have been a mainstay of cancer treatment for nearly 25 years, with over 40 approved across solid and hematological malignancies [Druker, 2025; Roskoski, 2024]. The introduction of IMA and subsequent 2nd-generation (2G) TKIs targeting the ATP-binding site of *BCR::ABL1*, such as dasatinib, nilotinib, and bosutinib, has led to a shift in the disease journey, bringing life expectancy for patients with CML close to an age-matched population [Schoepfer, 2018; Braun, 2020; Druker, 2025]. Few believed that an even more effective treatment was possible.

Yet, while these drugs have significantly improved outcomes for a once-deadly disease, over half of newly diagnosed patients don’t reach major molecular response (MMR) with IMA or 2G-TKIs and have discontinuation rates as high as 14% in the first year of treatment [Brümmendorf, 2022; Kantarjian, 2010]. Moreover, limited selectivity of these medications (eg, due to structural similarities in the ATP-binding site across kinases), frequently results in off-target effects that can impair short- and long-term safety and tolerability and have a persistent impact on quality of life [Sunder, 2023; Schoepfer, 2018; Clements, 2023]. In addition, patients are susceptible to developing resistance mechanisms, leading to an unsatisfactory response to therapy and increasing the risk of disease progression [Braun, 2020; Eide, 2015; Marin, 2010; Brümmendorf, 2022].

SCEMBLIXÒ (asciminib) represents a potentially transformative advance in CML treatment, not only as a therapeutic innovation but as a scientific milestone. It is the first and only approved allosteric inhibitor targeting ABL1 with an advanced, novel mechanism of action [SCEMBLIX PI]. Unlike all prior TKI treatments, which inhibit *BCR::ABL1* by binding to its ATP-binding site, SCEMBLIX binds to the myristoyl pocket of ABL1 kinase domain—a binding site unique to the *BCR::ABL1* oncoprotein—thus blocking ABL1 in its inactive conformation and mimicking its natural autoinhibition [Schoepfer, 2018; Wylie, 2017; SCEMBLIX PI]. The unique mechanism of action of SCEMBLIX enables high selectivity and potency, which maintains activity against the *BCR::ABL1* kinase domain mutations, including T315I, that confer the most common resistance to ATP-competitive TKIs, while reducing off-target effects and improving tolerability and safety [Schoepfer, 2018; Cortes, 2024]. The high potency and large therapeutic window of SCEMBLIX provides patients an opportunity to reach treatment goals, including MMR and deep molecular response milestones, faster and more frequently compared to the standard-of-care ATP-binding TKIs [Novartis Press Release, 12/8/2024; SCEMBLIX PI].

2) **Development & Clinical or Preclinical Evidence (500 words)**

History of the development of the solution/product\*

(please be as specific as possible in your description; 500 words)

Refusing to be satisfied with the status quo offered by IMA and 2G TKIs and believing that they could raise the bar even higher in CML treatment, a multidisciplinary research and development team at Novartis set out to overcome the limitations of available TKIs. Hantschel et al and Nagar et al in 2003 showed that a myristoyl group is involved in the autoregulation of ABL1 [Hantschel, 2003; Nagar, 2003], and an internal differential *BCR::ABL1* compound screen enabled Novartis researchers to identify a first set of compounds binding to this newly discovered myristoyl site. A novel nuclear magnetic resonance (NMR)-guided fragment screening and optimization approach was used to understand *BCR::ABL1* folding dynamics and guided the conversion of low affinity fragments to high affinity, biologically active lead compounds [Schoepfer, 2018; Zhang, 2010]. The Novartis research team recognized early on that inhibiting *BCR::ABL1* by an allosteric mechanism promised higher selectivity and the potential for better safety and tolerability of the drug [Schoepfer, 2018]. Importantly, it also promised activity against common *BCR::ABL1* mutations that confer resistance to IMA and 2G TKIs (eg, T315I), which could lead to overall higher efficacy [Schoepfer, 2018; Wylie, 2017]. Transforming the lead compound into SCEMBLIX (asciminib) demanded extensive work and innovative problem-solving, but after an 8-year effort, the first clinical trial of SCEMBLIX began in 2014 [ClinicalTrials.gov, NCT02081378].

SCEMBLIX was initially evaluated in the first pivotal study ASCEMBL (NCT03106779) as monotherapy for patients with CML-CP who had failed 2 or more prior TKIs, demonstrating superior efficacy and safety over the 2G TKI bosutinib in a setting where treatment options were limited [Rea, 2021]. Building on this success, SCEMBLIX then showed superior efficacy over both 1st- and 2nd-generation TKIs in newly diagnosed patients in the Phase 3 study ASC4FIRST (NCT04971226)—marking a significant advance in frontline therapy with the potential to redefine the standard of care [Hochhaus, 2024; SCEMBLIX PI].

In the ASC4FIRST trial, SCEMBLIX was the first therapy to be compared head-to-head with all standard-of-care TKI treatments. SCEMBLIX demonstrated statistically superior MMR rates at Week 48 (primary end point): 68% (95% CI, 61-74) vs 49% (95% CI, 42-56) for all Investigator-selected TKIs (IS-TKIs), and 69% (95% CI, 59-78) vs 40% (95% CI, 31-50) for IMA [Hochhaus, 2024; SCEMBLIX PI]. SCEMBLIX also showed a clinically meaningful, higher improvement in MMR rates by 15.1%, compared to 2G TKIs in the 96-week data presented at ASH 2024 [Novartis Press Release, 12/8/2024].

In ASC4FIRST, SCEMBLIX also demonstrated a 2-fold lower discontinuation rate and a reduced adverse reaction burden compared to ATP-binding TKIs. The most frequent adverse reactions observed across all treatment groups were hematologic (neutropenia, leukopenia, and anemia of Grade 3 or higher) which occurred less frequently with SCEMBLIX than with IMA and 2G TKIs [Novartis Press Release, 12/8/2024; SCEMBLIX PI].

As the first allosteric inhibitor that specifically targets the ABL myristoyl pocket (referred to as STAMP in the scientific literature), SCEMBLIX may represent a significant step forward in the treatment of CML—one that, in the opinion of many leading CML experts, is the most important advance since Gleevec [Novartis Press Release, 2/8/2021; SCEMBLIX PI].

**3) Innovation** (500 words)

Why this drug or device is innovative, the broad implications for future research, and/or how it will improve the human condition\*

TKIs are normally associated with multiple adverse reactions, which can make it hard for patients to live their normal lives [Sunder, 2023]. This can lead to skipped or reduced doses, which affect adherence to treatment and can result in suboptimal outcomes [Clements, 2023; Marin, 2010]. But SCEMBLIX has the potential to offer health care providers and patients a balance of efficacy and safety that may allow long-term disease management across patient populations [Hochhaus, 2024; Réa, 2021; Cortes, 2024; SCEMBLIX PI]. This includes older patients and those with more comorbidities, who have historically and preferentially been treated with IMA, and those with aggressive treatment goals and without comorbidities, who have been preferentially treated with 2G TKIs [Hochhaus, 2024; Réa, 2021; Cortes, 2024; NCCN CML V3, 2025]. With low discontinuation rates, and a reduced adverse reaction burden, SCEMBLIX enables more patients to stay on treatment [SCEMBLIX PI]. And when patients can stay adherent to SCEMBLIX, they are more likely to have deeper and more sustained molecular response rates, which in the long term would be expected to support an increased likelihood of treatment-free remission [Novartis Press Release, 12/8/2024].

Recognizing the persisting unmet need in CML, the potential of SCEMBLIX as a novel allosteric inhibitor of ABL, and its potential to achieve improvement over approved ATP-competitive TKIs, the US FDA prioritized and expedited its review. SCEMBLIX was granted 3 Breakthrough Therapy designations: for newly diagnosed CML, for 3L+ treatment in patients who had failed 2 or more TKIs, and as one of the few TKIs to demonstrate efficacy against the T315I mutation. It has received priority review status and accelerated approval twice across CML indications. In addition, SCEMBLIX was granted Real-Time Oncology Review status by the FDA Oncology Center of Excellence [Novartis Press Release, 2/8/2020; Novartis Press Release, 7/29/2024; Novartis Press Release, 10/29/2024; Novartis Press Release, 5/10/2024; FDA Press Release, 10/29/24].

With the FDA’s approval in October 2024 based on ASC4FIRST, SCEMBLIX is now approved for all CML treatment lines (newly diagnosed or previously treated or T315I mutated), signaling high regulatory confidence and a unique extrapolation-based approval strategy across all treatment lines. This offers physicians even greater flexibility when choosing a treatment for each patient’s unique CML journey [SCEMBLIX PI; NCCN CML V3, 2025].

To date, SCEMBLIX has been approved in over 75 countries [Novartis Press Release, 12/8/2024]. And within a month of its US 1L approval, the NCCN GuidelinesÒ recognized SCEMBLIX as a Category 1, Preferred treatment option for all newly diagnosed CML patients, reinforcing its clinical relevance and acceptance among leading oncology experts [NCCN CML V3, 2025].

At Novartis, expectations for SCEMBLIX are high, with ongoing studies in progress to explore and expand its utility so SCEMBLIX can help even more patients with CML at various stages of disease. Studies including ASC4FIRST (NCT04971226), ASC4START (NCT05456191), ASC4MORE (NCT03578367), and ASC2ESCALATE (NCT05384587) are focused on 3 key goals that have limited success with other TKIs: (1) improving deep molecular response rates, (2) improving treatment-free remission (TFR) success rates as well as time to achieve TFR, and (3) overcoming treatment-resistant mutations [ClinicalTrials.gov NCT04971226, NCT05456191, NCT03578367, NCT05384587].

SCEMBLIX has the potential not only to transform the treatment of CML, but also to offer a more hopeful future for patients. In the words of CML expert Dr. Michael Mauro (Memorial Sloan Kettering Cancer Center, NY): SCEMBLIX “offers hope that CML patients can respond better, have fewer side effects, and ultimately live free from cancer” [Grisham, 2025].

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