



Commercializing Cell and Gene Therapies

Overcoming the Barriers to Commercial Success

Jackson Carroll, Dr. Tony Xu, Krista Perry,

Christian Frois, Brenna Liponis, Alexander Fink

—

October 2019

EXECUTIVE SUMMARY

Six questions to ask when commercializing CGTs

Cell and Gene Therapy (CGT) is an exciting new frontier in the biopharmaceutical industry. The novelty of the technology and market introduces many complexities for companies commercializing CGTs. This white paper analyzes the challenges faced and outlines six key questions to consider for reducing complexity and supporting commercial success:

- 1**  Are we confident in the supply chain right up until administration of the treatment to the patient?
- 2**  Do we have the right pricing, reimbursement, and evidence model in place, not just the right price?
- 3**  Can we trace our product journey and understand every stakeholder that is involved in the delivery of our treatment?
- 4**  Do we have a field force that can manage the unique task of preparing the market and marketing the CGT treatment?
- 5**  Have we set the right expectations for the uptake of our CGT with our stakeholders?
- 6**  Have we identified how to build a platform that supports longer-term competitiveness in the CGT market?

While CGTs are treated as medical “products” for regulatory purposes, companies commercializing CGTs should build their strategy on supporting CGTs as a complete “treatment” to manage the complexities and differentiate their products.

OVERVIEW OF CELL AND GENE THERAPY

Growing number of therapies entering the market

Cell and Gene Therapies (CGTs) are a new, transformative category of therapies. Introducing human cells into a patient has been a part of healthcare for decades. Human-to-human blood transfusion has been recorded as early as 1818.¹ CGTs go a step further. Some CGTs involve the introduction of gene-modified cells into the body to significantly modify or even cure a specific disease.² Other CGTs involve the introduction, removal, or change in the genetic material in cells to treat an inherited or developed disease.³

Interest in the CGT field has grown steadily. In the 20 years between 1997 and 2017, there were only approximately 20 FDA-approved biologics license applications (BLAs) for cell-based therapies.⁴ Currently, there are over 1,000 ongoing CGT trials in 2019, the majority of which are for cell-based therapies.⁵ The FDA estimates that by 2025, there could be 20 new BLA approvals for cell therapy products *every year* in the US alone.

However, commercializing CGT treatments represents a new frontier for biopharmaceutical companies. Getting CGTs to patients presents significant complexities from supply and manufacturing to marketing and sales. This is particularly challenging for companies accustomed to the commercialization of small molecules and biologics.

TRINITY has worked with over a third of companies with CGTs on the market or in Phase III clinical trials across a broad range of commercialization topics, including business development, launch planning, evidence generation, market access, and pricing. Our experience in CGTs allows us to see first-hand the challenges experienced by companies and puts us in a unique position to identify considerations for commercial success.

¹ Pavenski, K., Saidenberg, E., Lavoie, M., Tokessy, M., & Branch, D. R. Red Blood Cell Storage Lesions and Related Transfusion Issues: A Canadian Blood Services Research and Development Symposium. *Transfus. Med. Rev.* 26, 68–84. (2012)

² American Society of Gene and Cell Therapy: Different Approaches. (2019)

³ FDA: What is Gene Therapy? (2018)

⁴ Yano, K., Speidel, A. T., & Yamato, M. Four Food and Drug Administration draft guidance documents and the REGROW Act: A litmus test for future changes in human cell- and tissue-based products regulatory policy in the United States? *J. Tissue Eng. Regen. Med.* 12, 1579–1593. (2018)

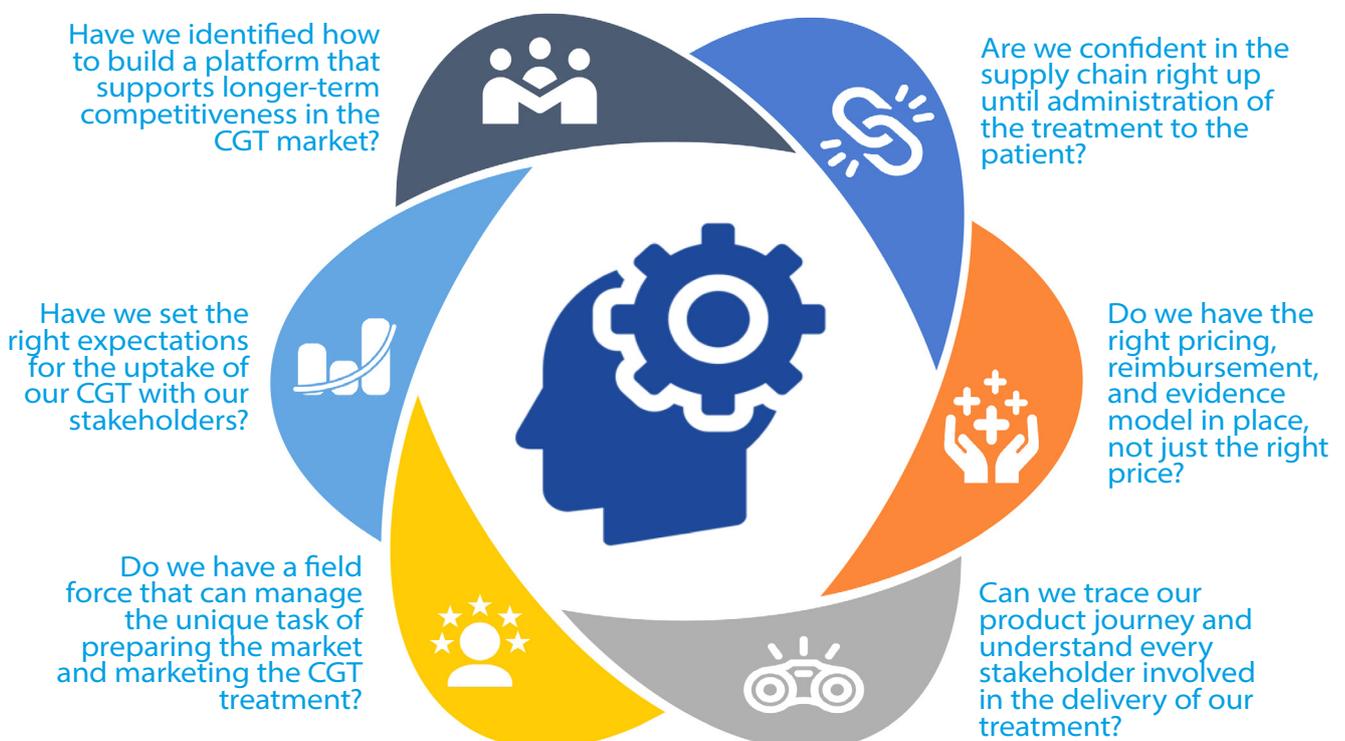
⁵ Alliance for Regenerative Medicine: Quarterly Global Regenerative Medicine Sector Report. (2019)

CONSIDERATIONS FOR A SUCCESSFUL COMMERCIALIZATION STRATEGY

Reducing complexities

The complexity of bringing CGTs to market requires new thinking and re-examination of old assumptions. Given the novelty of this market, there are no single silver-bullet solutions or established best practices. However, companies can reduce the complexity of commercialization by understanding the right questions to ask.

Specifically, companies commercializing CGTs should be able to answer the following six questions:



1



ARE WE CONFIDENT IN THE SUPPLY CHAIN RIGHT UP UNTIL ADMINISTRATION OF THE TREATMENT TO THE PATIENT?

Companies commercializing CGTs have often struggled to realize the full potential of their products due to the complexity of delivering these therapies at scale. As CGTs involve live human cells, or viral vectors, companies face challenges such as short shelf life, stringent storage and shipment conditions, region-specific safety and legal restrictions to shipping, and the need to establish traceability systems.⁶ CGT products generally need to be cryogenically frozen to ensure product integrity, adding overhead to shipping. Administration could be limited to centers regulated and approved by regulatory bodies (e.g. The Joint Accreditation Committee ISCT-Europe & EBMT [JACIE]), which may be far from the site of diagnosis, introducing potential barriers for delivery to the patient.

STRIMVELIS® availability was limited to one site in Europe due to complexities in manufacturing and delivery, requiring patients to potentially travel across borders for treatment. This complicated treatment for patients, confused HCPs on how to recommend the product, and delayed reimbursement approvals. Estimates suggest only five patients received Strimvelis since its 2016 launch, before it was sold to Orchard Therapeutics in 2018.⁷

These challenges are exacerbated in highly personalized CGTs, such as autologous CGTs where therapy is developed specifically for a single patient using the patient's cells, or allogeneic therapies using donor cells with systems to match cell lines to each patient.⁸ The personalization increases the lead-time, introduces variance in raw materials, and complicates scaling to meet commercial demand.

Additionally, reimbursement challenges can be exacerbated by the requirements of the supply chain. In many circumstances it is not defined how the CGT manufacturer gets compensated for services beyond the cost of the treatment (for example, capital expenditure and ancillary costs).

Companies launching CGTs should, therefore, **see the supply chain as a critical strategic concern**. The supply chain strategy should be considered before commencement of human clinical trials, to support selection of trial sites and, later, prioritization of treatment centers. Companies need to **conduct a detailed analysis of the end-to-end delivery at commercial scale**, to identify barriers not apparent at clinical stages, and focus on removing all the barriers up until patient administration. Often, custom solutions may be needed, such as custom dewars shared with the local center or algorithms for matching patients to treatment.

PROVENGE® commercialization hit a hurdle when the FDA expressed concerns on product traceability due to the complicated administration and logistical steps involved. Dendreon then invested ~\$5 million to develop a unique logistical and patient treatment management and planning system, which coordinates the patient and physician scheduling as well as the operational and logistic activities. Subsequently, the FDA was satisfied Dendreon had implemented required changes to product tracking procedures.^{9,10}

⁶ Levine, Bruce L et al. Global Manufacturing of CAR-T Cell Therapy. *Molecular therapy. Methods & clinical development*. vol. 4 92-101. (2016)

⁷ Tiny UK Biotech Takes On Glaxo's \$730,000 Gene Therapy. (2018)

⁸ Years of dreams about CARs turn into reality for Atara. (2019)

⁹ Dendreon Corporation Annual Report. (2009)

¹⁰ CMC review of Provenge. (2007-2010)

Companies might benefit from having a partner to help put the supply chain in place and operate it. However, there needs to be clear criteria for identifying the right partner, such as whether the potential partner has the right technology for transporting CGTs and the right experience in target markets. The importance of the supply chain to commercial success means that there must be complete confidence in the selected partner.

Supply chain strategy is a top strategic concern for companies commercializing CGTs; planning needs to happen early enough to accommodate time for implementation. Executives in these companies should challenge themselves to be able to answer positively to the question: Are we confident in the supply chain right up until administration of the treatment to the patient?

2



DO WE HAVE THE RIGHT PRICING, REIMBURSEMENT, AND EVIDENCE MODEL IN PLACE, NOT JUST THE RIGHT PRICE?

CGTs have large cost of goods and are some of the most expensive products on the market. This creates challenges with developing a pricing and reimbursement model that is accepted by stakeholders.

Payers struggle with the financial risk of a high upfront cost for a product with, at the time of launch, uncertain durability of efficacy due to the lack of long-term outcomes, and possibly other trial data limitations often due to the rarity of the target population for treatment. With a potential upfront cost of more than one million dollars and typically no specific health technology assessment (HTA) or funding pathway to accommodate these concerns, the situation can be particularly challenging for payers. At such prices, physicians', patient advocacy groups' (PAGs), and patients' enthusiasm for using the product cannot be taken for granted. We have already seen in some HTA/pricing negotiations key opinion leaders (KOLs) and PAGs opposing providing access to new therapies for fear that this access comes at the cost of other therapies. Hence, having a submission and negotiation approach that fails to resonate with stakeholders could undermine a promising therapy.

Companies should, therefore, have a carefully considered and integrated pricing and reimbursement approach. While the approach will need to be adapted to each country and ultimately each payer, a few considerations are common. The approach should help alleviate key payer concerns associated with CGTs including their potential upfront negative impact, the durability of treatment efficacy, and turnover of the insured (for non-single national payer systems as in the US, Germany, etc.). Companies may need to consider financing options to share payer risks and smooth payer investment over time, such as offering outcome-based payment, and pay-by-installment options.

To overcome payer reservations for KYMRIA[®] in Italy, Novartis developed an innovative “payment at results” approach that involved three separate payments to the company. Each payment will be made only if the therapy is shown to be effective. If it is not effective, Novartis will cover the treatment costs. Novartis has since secured reimbursement for Kymriah in Italy on the basis of this approach.¹¹

Manufacturers may also need to consider providing patient financing to patients who need to cover some of the cost of treatment themselves. While these options offer a tailored response, they often

¹¹ Bluebird: on a mission to 'recode' the DNA of healthcare. (2019)

come with their challenges both for the manufacturer (e.g. alignment with meaningful outcome measures while mitigating risk and setting up the supporting infrastructure) and for the payer (e.g. policy coordination with other country payers). To be ultimately successful in payer negotiations, manufacturers will need to pursue an approach integrating the right pricing and access model with the appropriate evidence, physician and expert support, and patient advocacy.

Another critical question to consider is the sustainability of the model. With over 1,000 ongoing CGT trials in 2019 and significant affordability and prioritization challenges for global payers pending, payers may be forced to consider radical changes in how they fund such innovation. The creation of special funds and reinsurance pools for CGTs, similar to what the UK did for cancer drugs, is likely, and manufacturers will need to consider their position regarding such initiatives.

For more details, please also see our recent publication [“Exploring the Truth of Reimbursement: Challenges for Cell and Gene Therapies.”](#)¹²

3

CAN WE TRACE OUR PRODUCT JOURNEY AND UNDERSTAND EVERY STAKEHOLDER INVOLVED IN THE DELIVERY OF OUR TREATMENT?



Commercial adoption of CGTs is critically dependent on an extensive network of stakeholders. These stakeholders may experience challenges, not directly related to the clinical properties of the product, that inhibit them from supporting the commercialization of CGTs.

The challenge of administering a CGT is particularly evident in CGT treatment centers. Due to the novelty of the technology, administration of CGTs requires numerous professionals at the local center to be specially trained and certified, creating significant administrative challenges for the centers trying to adopt the new CGT therapy.

MEMORIAL SLOAN KETTERING CANCER CENTER faced significant administrative complexity when adopting chimeric antigen receptor T-cell therapy (CAR-T), due to the number of stakeholders that needed to be involved. This includes administrative, nursing, and financial advisory staff to facilitate intake and pre-screening, physicians certified with both the institution and the manufacturer to provide consultation, apheresis personnel and cell therapy technologists to process CAR-T therapy products, pharmacist and billing and reimbursement staff familiar with specific protocols for CAR-T therapy, intensive care specialists educated on CAR-T therapy specific toxicities, and data management personnel for obligatory data reporting on outcomes.¹³

Regulators require a traceability system for CGTs involving tissues or cells to ensure each unit of the product can be traced from the donor or source material to the patient and vice versa.¹⁴ Additionally, the requirement for safety follow-up may extend to the patient's family and close contacts. These requirements necessitate significant investment from both manufacturers and treatment centers and could delay adoption of the therapy.

¹² TRINITY White Paper: [Exploring the Truth of Reimbursement Challenges for Cell and Gene Therapies](#). (2019)

¹³ Perica, K., Curran, K. J., Brentjens, R. J. & Giralto, S. A. Building a CAR Garage: Preparing for the Delivery of Commercial CAR-T Cell Products at Memorial Sloan Kettering Cancer Center. *Biol. Blood Marrow Transplant.* 24, 1135–1141. (2018)

¹⁴ EMA: Guideline on safety and efficacy follow-up and risk management of advanced therapy medicinal products. (2008)

Some stakeholders may not have the right understanding of the treatment due to the novelty of the technology. Physicians may also be unwilling to prescribe or refer a patient for CGT treatment because they are unaware of the treatment, unsure of how to identify eligible patients, or do not believe in the technology. Patients may decide not to have the treatment because of emotional barriers, including the risk of unfamiliar side effects of the therapy. Equally challenging is supporting patients who expect CGT treatments to be as widely available as typical drug products and who then become frustrated when they cannot access the treatment.

Companies commercializing CGTs **need to think beyond the delivery of a product and adopt a mindset of delivery of a treatment to identify the holistic set of stakeholders involved in administration and post-delivery care.** This would enable companies to engage with identified stakeholders early to understand potential barriers and determine possible solutions.

The solutions involve offering a service beyond drug discovery, such as training and certification of medical personnel, helping patients identify treatment centers, supporting establishment of reimbursement systems, or providing an IT system for product tracking. Companies will need to plan and invest early to be able to offer such services.

4

DO WE HAVE A FIELD FORCE THAT CAN MANAGE THE UNIQUE TASK OF PREPARING THE MARKET AND MARKETING THE CGT TREATMENT?



Given the need to fully engage key stakeholders at the local treatment center, CGTs require a different type of field force to support the critical activities associated with commercializing the treatment. The role of the field force is more than building awareness for the therapy.

YESCARTA[®] administration requires staff at local treatment centers to be specifically trained and certified. To facilitate the process, Kite Pharma created a multidisciplinary field team to provide education, logistics training, and site certification.¹⁵

CGT Medical Science Liaisons (MSLs) must be highly educated in the relevant fields to be able to discuss very complex questions, often while having little data at hand. They can help identify meaningful patient outcome measures to validate treatment success, which may be critical for market access, and inform how to manage potential safety concerns not visible from small population trials. CGT Field Market Access and Key Account Managers (KAMs) need to be well versed in both economics and the processes within each hospital. They are first-line service providers to help the stakeholders set up the infrastructure required to adopt the product, such as technology training, patient identification, personnel and site certification, and technology system implementation.

Companies **need to consider carefully how much time and effort is necessary to find, hire, and train the field force.** Compared to traditional biopharmaceutical companies, companies commercializing CGTs may need to work more closely with their field force to ensure they have the necessary tools. They must be able to confidently answer that they have the field force to manage all the activities associated with commercializing the CGT treatment. Given the challenges of finding the right people, companies must also consider how to retain the acquired talent.

¹⁵ FDA Approves Gilead CAR-T Therapy Yescarta, Plans Regenerative Medicine Policy 'Soon'. (2017)

5



HAVE WE SET THE RIGHT EXPECTATIONS FOR THE UPTAKE OF OUR CGT WITH OUR STAKEHOLDERS?

CGTs could have a very different forecast from existing biopharmaceutical therapies owing to their unique properties. Compared to biopharmaceuticals used in management of chronic conditions, CGTs often target a smaller patient population, for a single treatment. CGTs also have fewer analogs to guide the forecast. And because of the novelty of the technology and the complexities with commercialization of CGTs, the uptake could be slower than that of other biopharmaceutical therapies.

Companies commercializing CGTs need to help stakeholders both internal, such as company board members, and external, such as investors and patients, set the right expectations on uptake of the treatment. Potential uptake scenarios need to be carefully considered and presented during initial discussions around commercialization with company boards and investors. Companies should be prepared to help the board and investors understand the expected challenges around managing revenue versus costs. Companies must also be prepared to help stakeholders fully understand the complexities of CGT commercialization to gain an appreciation for the uptake scenarios presented. This includes setting expectations based on anticipated price and how much a patient might need to pay out-of-pocket. Companies should also engage with patients to keep them updated on when and where the treatment is available. This is particularly important for therapies that are only effective before a certain age.

Additionally, the pipeline structure required for a sustainable CGT portfolio may be very different from that of other biopharmaceutical therapies. Companies need to ensure stakeholders are aligned to provide adequate investment into the broader portfolio.

6



HAVE WE IDENTIFIED HOW TO BUILD A PLATFORM THAT SUPPORTS LONGER-TERM COMPETITIVENESS IN THE CGT MARKET?

Given the complexities of commercializing CGTs and the novelty of the market, many companies need to collaborate across the value chain, including research, supply chain and manufacturing, and marketing and sales. However, compared to more traditional biopharmaceuticals, the commercial success of a CGT treatment is more critically dependent on competencies across and beyond the provision of the treatment. Hence companies should have a clear view of what needs to be preserved in-house to have more flexibility to implement process improvements and to protect core competences. These could include specific cell processing technology, specific manufacturing capability, or a unique patient tracking and logistic system.

Because best practices and technologies are yet to be established, companies need first to identify what areas they need to build. Companies need to understand which of these areas they need to develop themselves, and where collaborating with other companies could help. When evaluating collaboration options, companies should critically assess whether they have found the right partner with the right capabilities and an agreement that offers acceptable flexibility.

CONCLUSION

Key considerations for commercializing CGTs



Companies commercializing CGTs should focus on reducing complexities with commercialization to achieve commercial success.



CGT companies should be able to answer and identify tailored solutions for the critical questions asked during commercial planning.



The commercialization strategy should be centered on developing a treatment that goes beyond the product itself. While CGTs are considered as medical products for regulatory purposes, their commercialization is more akin to that of a full medical treatment.



The CGT market is only just emerging, giving companies the opportunity to establish best practices and build competitiveness for long-term success.



AUTHORS



Jackson Carroll
Principal | Munich

Jackson has 17 years of consulting experience and a strong business background. He has undertaken strategic analysis, assessment of new opportunities, launch support, forecasting, business planning and organizational redesign for leading pharmaceutical and healthcare companies in Europe. Jackson's consulting experience is in diverse therapeutic areas including diabetes, oncology, and hemophilia and has worked for clients in the UK, US, Turkey, Thailand, and over 15 European countries.

Before joining TRINITY, Jackson worked with McKinsey & Company, ZS Associates, Syneos Health Consulting, and Accenture, as well as working as a freelance strategy consultant for life sciences and pharmaceuticals firms in Europe. Jackson earned an MBA (with Distinction) from London Business School and a Bachelor in Information Technology from The University of Queensland in Australia.



Dr. Tony Xu
Sr Consultant | Munich

Tony has rich experience in a range of commercial strategy topics developed through working with large global pharmaceutical companies as well as emerging biotechnology companies. His consulting projects include developing a 2025 global business model, an EU launch strategy through strategic market segmentation and detailed understanding of the patient journey, a launch plan for Europe, a 2020 global payer strategy, and a portfolio expansion strategy. Tony currently lives in Munich but has previously spent extended periods of time in London and Shanghai.

Before joining TRINITY, Tony worked with Sanofi, A.T. Kearney, and Syneos Health Consulting. Tony combines business with science by earning a full scholarship PhD in Pharmacology from The University of Cambridge and has several scientific publications.



Krista Perry
Principal | San Francisco

Krista supports biopharma and biotech companies in their Business Development (BD) and commercialization strategy. Krista joined TRINITY in 2006 and co-leads the San Francisco office. Krista partners with companies focused on commercial assessments, BD/ Non-Personal Promotion (NPP) strategy, pipeline/portfolio prioritization and strategy, and launch roadmap planning, bringing deep experience in rare diseases. Clients leverage Krista's insights in navigating early-mid clinical-stage product development opportunities and the commercial needs required to recognize their full potential, including: analog analyses, forecasting, market research, licensing & acquisition opportunities, and cross-functional strategy & alignment.

Krista earned her psychology and premed degree from Dartmouth College.



Alexander Fink
Managing Partner Europe | Munich

Alexander has more than 20 years of experience in strategy consulting, and over that time he has advised more than 70 clients in over 300 strategic assignments covering all continents and more than 40 countries. He advises life sciences executives and investors on complex issues that require strong content expertise and analytical rigor paired with a deep understanding of what it takes for success in the life sciences industry. Alexander lives in Munich and works globally with his clients, after having spent extended periods of time in New York, Johannesburg, and Jakarta. Before joining TRINITY, Alexander worked in Principal and Partner positions with companies such as Monitor Group, Roland Berger, and Syneos Health Consulting. Alexander has studied business administration in Germany, the UK, and the US.

Christian Frois
Principal | Waltham

Brenna Liponis
Engagement Manager | Munich

For more information or if you have any specific questions, please contact:

Jackson Carroll at jcarroll@trinitylifesciences.com or

Alexander Fink at afnk@trinitylifesciences.com



About TRINITY

TRINITY is a trusted strategic partner, providing evidence-based solutions for the life sciences. With over 20 years of experience, TRINITY is committed to solving clients' most challenging problems through exceptional levels of service, powerful tools, and data-driven insights. TRINITY's range of products and solutions includes industry-leading benchmarking solutions, powered by TGaS® Advisors. TRINITY, together with its subsidiary TGaS Advisors, has 5 offices throughout the US, including Boston, New York, Princeton, Philadelphia, and San Francisco, as well as Toronto, Canada, Gurgaon, India and Munich, Germany. To learn more about how TRINITY is elevating life sciences and driving from evidence to action, visit trinitylifesciences.com.

Contact TRINITY

EUROPE

Widenmayerstr. 50
80538 Munich, Germany

[T] +49 89 2388557 90

CORPORATE HEADQUARTERS

230 Third Avenue
5th Floor
Waltham, MA 02451-7528

[T] +1 781-577-6300