T-Cell Therapies: Building an ecosystem to maximise success.
About CGT Catapult

Part of a **world-leading network** of technology and innovation centres

Provide access to unique technical **facilities** and **expertise** to help adopt, develop and exploit innovations

**Bridge the gap** between businesses and academic research

Established by Innovate UK as a **not-for profit**, independent centre

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It is our vision for the **UK** to be a **global leader** in the development, delivery and commercialisation of cell and gene therapies.

Where businesses can start, grow and **confidently develop** advanced therapies, delivering them to patients rapidly and effectively.
**CGT Catapult Capability:**

<table>
<thead>
<tr>
<th>Accelerate</th>
<th>Complement</th>
<th>Innovate</th>
<th>Facilitate</th>
</tr>
</thead>
<tbody>
<tr>
<td>the commercialisation of innovations from research</td>
<td>industry and academia with unique technical facilities and expertise</td>
<td>in collaboration with academia and industry</td>
<td>operating in UK as a global centre; working with Government, the NHS and international regulators</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Development laboratories</th>
<th>Manufacturing centre</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 1200m² purpose built centre</td>
<td>- 7000m² manufacturing centre designed specifically for cell and gene therapies</td>
</tr>
<tr>
<td>- Analytical characterisation</td>
<td>- 12 segregated large clean room modules</td>
</tr>
<tr>
<td>- Process development</td>
<td>- Secure supported collaboration model</td>
</tr>
<tr>
<td>- Viral vector</td>
<td>- Centre of a cell and gene therapy cluster</td>
</tr>
</tbody>
</table>

**Cell and gene therapy specialists (>180)**

<table>
<thead>
<tr>
<th>Industrialisation</th>
<th>Regulatory and clinical development</th>
<th>Engagement</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Process development</td>
<td>- Regulatory</td>
<td>- Collaboration formation</td>
</tr>
<tr>
<td>- Analytical development</td>
<td>- Non clinical safety</td>
<td>- Intellectual property and patent</td>
</tr>
<tr>
<td>- Manufacturing systems</td>
<td>- Clinical delivery</td>
<td>- Health economics</td>
</tr>
<tr>
<td>- Supply chain</td>
<td>- Programme management</td>
<td>- Reimbursement</td>
</tr>
</tbody>
</table>
Breaking down industry barriers

Manufacturing and supply chain
- Ability to scale up cost effective, robust and reliable manufacturing
- Meaningful quality and analytical assays
- Specificity of storage and delivery systems

Regulatory and clinical framework
- Uncertain, complex regulatory environment
- Clinical trial site ability to handle live products
- Cautious hospital research committees

Health economics
- Uncertainty on reimbursement
- Poorly understood health economics
- Unproven business models
Industrialisation

The challenge

Developing a reliable and robust manufacturing process.

How we can help

Identifying ways to lower the costs of manufacturing your product.

Finding innovative ways to make your process more efficient and robust.

Providing methods to accelerate and support clinical trials.

Helping ensure your process and product are controlled and quality compliant.

Using tried and tested methods to transfer seamlessly to Good Manufacturing Practice (GMP) manufacturing.
The Industrialisation Team - Our team is your team

- Cell Characterisation
- Potency Assay Development
- In-Process Controls
- Data Mining and Informatics

- GMP Compliance
- GMP Knowledge Base
- CMC
- Documentation

- Design Space
- CPPs for CQAs
- Scale-up / Automation
- Closed Processing
- In-Process Controls
- Process Economics
- Device Design

- Vector Design / Optimisation
- Large Scale production
Maturation of the cell and gene therapy field
Maturation of the ATMP Field

<table>
<thead>
<tr>
<th>Product</th>
<th>Price</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yescarta</td>
<td>$373,000</td>
<td>(axicabtagene ciloleucel) Kite’s CAR-T therapy for forms of Diffuse large B-cell lymphoma (DLBCL) in adults. Type of non-Hodgkin lymphoma (NHL).</td>
</tr>
<tr>
<td>Strimvelis</td>
<td>€600,000</td>
<td>GSK’s treatment for a very rare disease called ADA-SCID (Severe Combined Immunodeficiency due to Adenosine Deaminase deficiency),</td>
</tr>
<tr>
<td>Kymriah</td>
<td>$475,000</td>
<td>(tisagenlecleucel) Novaritis’s CAR-T therapy for B-cell precursor acute lymphoblastic leukemia (ALL) in children and young adults.</td>
</tr>
<tr>
<td>Glybera</td>
<td>&gt;€1,000,000</td>
<td>(alipogene tiparvovec) UniQure’s AAV-based gene therapy to treat the rare inherited disorder lipoprotein lipase deficiency (LPLD)</td>
</tr>
</tbody>
</table>
## State of Play in the EU – Since Regulation (EC) 2007/1394

<table>
<thead>
<tr>
<th>Product</th>
<th>Status and Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imylic</td>
<td>Approved 2015</td>
</tr>
<tr>
<td>Holoclar</td>
<td>Approved 2015</td>
</tr>
<tr>
<td>Strimvelis</td>
<td>Approved 2016, 2 patient treated – patients go to Italy for treatment</td>
</tr>
<tr>
<td>Zalmoxis</td>
<td>Approved 2016, Conditional MA</td>
</tr>
<tr>
<td>Spherox</td>
<td>Approved 2017</td>
</tr>
<tr>
<td>Alofisel</td>
<td>Approved 2018</td>
</tr>
<tr>
<td>Yescarta</td>
<td>Approved 2018</td>
</tr>
<tr>
<td>Kymriah</td>
<td>Approved 2018</td>
</tr>
<tr>
<td>Chondroselect</td>
<td>Voluntary Withdrawal 2016</td>
</tr>
<tr>
<td>MACI</td>
<td>Approved 2013, Suspended 2014 (Manufacturing Discontinued)</td>
</tr>
<tr>
<td>Provenge</td>
<td>Approved 2013, Withdrawn 2015</td>
</tr>
<tr>
<td>Glybera</td>
<td>Approved 2012, 1 patient treated</td>
</tr>
</tbody>
</table>
Immuno-Oncology Sector – The Next Generation!

*Adapted from the original presented at Wells Fargo Securities Healthcare Conference, Nov 2017

Need to deliver scalable, low cost manufacturing solutions to enable healthcare provider adoption of a diverse portfolio of therapies.
What key factors influence therapy price?

Key Cost Contributors – Product Manufacture and Administration

Key Cost Contributors – Perceived / Tangible value to the Healthcare System

- Can be very challenging to define
- What is the true cost (lifetime cost) of a patient to the healthcare system
- How do you engage a patient for their lifetime, especially if they are cured within a year?
Shaping your development program to address areas of need.
Understanding your product

**Target Product Profile**
Indication, treatment, delivery mode, dose, formulation efficacy, side effects

**Quality Target Product Profile**
Quality characteristics to ensure safety and efficacy as promised in the label

**Critical Quality Attributes**
A physical, chemical or biological, property that should be within an appropriate limit, range to ensure product quality

**Critical Process Parameters**
Process parameter whose variability should be monitored or controlled to ensure the process produces the desired quality
Understanding the needs of your stakeholders

**Stakeholders**
- Clinic
- Investors
- Regulators
- Manufacturing

**Process Diagnostics**
- Short Term
- Phase I/II Clinical Trials
- Long term

**Commercialisation**

**Process / Manufacturing Development**

**Risk to Patient / Product Variations / Failed Manufacture**
- Not Cost Prohibitive
- Safety / Understanding / Control
- Design Space / Robust and Reproducible

**Ease-of-use**
- Economic/ Commercial Viability
- Full Characterisation / GMP Compliance / IPCs
- Automation and High-Throughput
Understanding your process

Process Mapping

Areas of process currently undefined

Ishikawa

Root Cause of Failure

FMEA

Risks and Mitigation Strategies

Facility Utilisation and CoGs

Facility Utilisation Profile
Accelerating your program development

**Structure**
- **Structured Development Program to meet Clinical Objectives**
  - Strategic development appropriate for clinical phase
  - Decrease time to pre-clinical & clinical studies
  - Focus on high priority areas

**Risk**
- **Reduce the risk of an expensive, failed GMP Manufacture**
  - Financial Risk – Batch losses; Future investment
  - Reputational Risk – Company; Clinical uptake

**£**
- **Reduce costs of the Development Program and GMP manufacture**
  - Decrease CoGs / Increase the probability of achieving the reimbursement price-point
  - Dendreon (Provenge) – Manufacturing CoGs up to 77% of $94,000 price tag.
  - TiGenix (Chondroselect) – Poor uptake in key markets – Reimbursement challenges
Manufacturing Development Challenges: Key Factors Shaping the Field
Autologous vs Allogeneic – The Concepts

- “Made-to-order”
- Patients own cells are the starting material
- Potential to utilise some blood processing technologies, but lack of technology solutions in general.
- COGs structure is driven by facility throughput capability.

- Off-the-shelf use
- Cell bank based
- Potential to use established biopharma processing technologies
- Scalable COGs structure and spread across multiple doses and therapeutic targets.
Scaling Manufacture

Scale - Out

Autologous
Each reactor contains a single patient’s therapy

Scale - Up

Allogeneic
Each reactor contains enough doses to treat thousands of patients
Key factors for consideration

Raw Material Supply
(e.g. Adventitious agent Testing/Supply agreements/licensing)

Closed Processing
(e.g. Technology Selection/Room grade)

Automation
(e.g. Throughput/accuracy/reproducibility/operator error reduction)

Adaptive Control
(Process robustness and reduced failure rates)

Process Control
(e.g. in line analytics / visual observation removal)

Scalability
Needs of the clinic versus needs of the market / Skilled work-force

Intermediate / Product Stability
Manufacturing strategy / Clinical population needs

Data Integrity and Storage
(e.g. Electronic Record Keeping and Tracking)

Facility Throughput

Clinical Handling
(Specialised thaw-at-site systems)
Automation Strategies for Autologous Therapies

1 Open static

- Patient Material
- Incubator
- Cell Therapy

2 ‘Bolt Together’

- Patient Material
- Device 1
- Device 2
- Device 3
- Cell Therapy

3 Integrated

- Patient Material
- Integrated Platform
- Cell Therapy

4 High Throughput

- Patients Materials!
- High Throughput Platform
- Cell Therapies!

Increasing integration + automation $\rightarrow$ increased facility throughput

Increasing integration + automation $\rightarrow$ decreasing cost of goods
Example of a “Bolt-Together” Solution

“Bolt-Together” Solutions

Multiple technologies linked together

Each technology is only used for the duration it is required during the process.

Typically analytics are off-line / limited in-line measurements (DO/pH etc).

Still heavily manual in nature – operator is required to move material from system to system

Supports flexibility in process design

CGT Catapult Focus - Developing Centralised Control Systems
Example of an “Integrated” Solution

Integrated Solutions

Each reactor contains a single patient’s therapy

Each system is “dedicated” for the duration of the process

Typically analytics are off-line / limited in-line measurements (DO/pH etc)

Cocoon™
(Octane & Lonza)

Prodigy®
(Miltenyi)
Example of “High-Throughput” Vision

**High Throughput Solutions**

- System is modular in nature allowing segregation of processing bottlenecks.
- Each reactor contains a single patient’s therapy
- Each system is capable of processing multiple patient therapies concurrently.
- Analytics are on-line / in-line and feed into decision making algorithms.

**CGT Catapult Focus**

- Development of enabling technologies to support high-throughput concepts.
Manufacturing Development for a TCR therapy

**Process A**
- Starting Material
- Blood leukapheresis
- Bag Centrifugation
- Cell Wash, Concentration and Selection
- Dynabeads
- Seeding and Activation
- Retronectin coating
- Viral vector loading (Centrifugation)
- Transduction

**Process B**
- Process Changes
  - Hold
  - Bag Centrifugation
  - Reduction in number of cell washes and addition of hold and filtration steps to mitigate risk of cell aggregation
  - Automation of cell washing and concentration. Plus addition of controlled cell impurity removal (RBC lysis)
  - Introduction of automated cell selection and resuspension into cell expansion media.
  - Switch of activation agent to remove need for de-beading step.
  - Scale of operation increased to reduce manual handling.
  - Removal of centrifugation based vector loading.
  - Removal of requirement for vector pre-loading.
  - Reduced vector usage as a function of reduced seeding densities (required higher conc. Vector).
  - Reduction in WV to improve efficiency of transduction.

**Process C**
- Process Changes*
  - Blood leukapheresis
  - Bag Centrifugation

*Changes constrained by on-going clinical trial
Manufacturing Development for a TCR therapy

**Expansion**
- Day 4: IL-2 spike, Dynabead removal, Feeding
- Day 5: IL-2 spike, Dynabead removal, Feeding
- Day 6: IL-2 spike, Feeding
- Day 7 (Green): Feeding, Transfer to DC3000
- Day 8: Feeding

**Cell Wash & Concentration**
- Day 7 (Green): Bag centrifugation, Formulation & Freezing
- Day 10 (Blue & Orange): Bag centrifugation, Formulation & Freezing

**Formulation & Freezing**
- Day 4: Bag centrifugation
- Day 5: Bag centrifugation
- Day 6: Bag centrifugation
- Day 7 (Green): Bag centrifugation
- Day 8: Bag centrifugation

- Automation of cell washing and conc.
- LOVO

- Additional bead removal step introduced to ensure depletion from final product.
- Scale of operation increased to reduce manual handling.
- IPCs put in place around Dynabead removal and alternative assay for bead detection developed.
- Additional feed required, but combined with IL-2 spike to support reduced days of intervention.
- Cell formulation changed to support reduced final product volumes.
- Additional feed required, but combined with IL-2 spike to support reduced days of intervention.
- Scale of operation increased to reduce manual handling.
- Scale of operation increased to reduce manual handling.
Logistics by Design

Creating a Framework to Support ATMP Commercialisation
Why do we need a Framework?

“Surely it’s just a case of picking up the phone and “voila”, next day delivery”

*Unfortunately not - the logistics complexity surrounding ATMP manufacture and subsequent connection of final product to patient requires significant planning!*

Logistics success will be influenced and impacted by several key stakeholders both internal and external to the therapy developer throughout the development lifecycle.

**To be successful, the vision for a commercial logistics strategy needs to be planned early & have quality designed-in from the start.**
Logistics – How complex can it be?

Autologous CAR-T Immunotherapy – a simplified example of key shipments that may form part of the therapy’s value chain

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apheresis</td>
<td>3200 @ controlled ambient(?)</td>
</tr>
<tr>
<td>Product</td>
<td>6400 @ LQN Dryshipper</td>
</tr>
<tr>
<td>QC</td>
<td>320 shipments (x No. of different QC sites)</td>
</tr>
<tr>
<td>Raw Material</td>
<td>10 – 50 @ -80°C</td>
</tr>
<tr>
<td>Patient Samples</td>
<td>2 a year x 3200 = 6400</td>
</tr>
<tr>
<td></td>
<td>Track for 15 years, by year 15 you are doing</td>
</tr>
<tr>
<td></td>
<td>2 x 3200 x 15 = 96000 a year!!</td>
</tr>
</tbody>
</table>
Logistics - What could possibly go wrong?

STABLE THERMAL PACKAGING

SENSOR + COMMUNICATION EMBEDDED PACKAGING

SECONDARY THERMAL PACKAGING for SITE LOCAL TRANSPORT to BEDSIDE

DEDICATED THERMAL PACKAGING FLEET
Logistics - What could possibly go wrong?

**Excursion Statistics**

<table>
<thead>
<tr>
<th>Type</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Alarm Threshold</td>
<td>15.0</td>
</tr>
<tr>
<td>Total Time Below</td>
<td>944h</td>
</tr>
<tr>
<td>Longest Low Threshold</td>
<td>944h</td>
</tr>
<tr>
<td>High Alarm Threshold</td>
<td>23.0</td>
</tr>
<tr>
<td>Total Time Above</td>
<td>898h</td>
</tr>
<tr>
<td>Longest High Threshold</td>
<td>898h</td>
</tr>
</tbody>
</table>

**Unique Challenges Posed by Cell and Gene Therapy Logistics and Packaging**

- Manufacturing
- Site
- Patient
- Logistics provider
- Logistics vehicle
- Data integrator
- Qualified person
- To name a few...

**Automated Data Analytics**

**Real Time Systems Integrations with Partners**
Logistics - What could possibly go wrong?

AIRLINE RESTRICTIONS ON COMMUNICATION SYSTEMS

MANAGEMENT of TIME SENSITIVE SHIPMENTS

CLEANLINESS OF PACKAGING
Logistics is more than just physical material movement.
As early as possible – Logistics should have lifecycle management plans similar to clinical and manufacturing development
Logistics by Design – Build in Quality from the Start

**Quality by Design**

- TTP
- QTPP
- CQA
- CPP
- Identify Design Space
- Control Strategy
- Process Validation & Monitoring

---

**Logistics by Design**

- TLP
- FTLP
- CLA
- CLP
- Identify Design Space
- Control Strategy
- Logistics Validation & Monitoring

---

**Target Logistics Profile**
- Overarching objectives of a commercial logistics strategy with respect to supporting business goals, supplying market needs, maintaining regulatory compliance and facilitating clinical adoption.

**Focused Target Logistics Profile**
- Prospective summary of the commercial logistics strategy traits that need to be achieved for all components of the value chain, to ensure successful delivery of product to patient whilst maintaining chain of custody and identity.

**Critical Logistics Attribute**
- A physical, temporal, informatic or operational property that needs to be within an appropriate limit, range, distribution or tracked and traced, to ensure the desired logistics strategy is fulfilled.

**Critical Logistics Parameter**
- A logistics parameter whose variability or failure would impact a critical logistics attribute and therefore should be monitored or controlled to ensure the desired logistics strategy is fulfilled.

**Identify Design Space**
- The design space or operating ranges for the CLPs are elucidated through practical assessment using supporting tools, such as Design of Experiments (DoE) or through the testing as part of logistics development activities.

**Control Strategy**
- A planned set of controls, derived from current logistics understanding that ensures service performance and quality. Controls may include parameters and attributes related to physical or informatic characteristics and include frequency of monitoring and control.

**Logistics Validation and Monitoring**
- A MAA/launch ready logistics system functional on a global footprint with regular performance review to support real time data driven decision making to further optimise the logistics undertaking.
Identifying root cause failures of the planned logistics strategy 

Examples of Route Cause Failures 

- Storage Requirements 
  - Controlled Ambient
  - Defined Window

- Just in Time
  - On the shelf

- Unplanned event
  - Temperature:
    - -196°C to 2°C
    - 2°C to 8°C
  - Controlled Temp Packs

- Monitoring and Control
  - Proximity to Product/Sample
  - Labeling

- Planning and Implementation
  - Courier
  - Single Provider
  - Sub-contracted

- Chain of Custody Management
  - Management
  - Chain of Custody
  - Tracking Devices

- Clinical Site
  - Manufacturing Site
  - Data Management Provider

- Marketing Licence Approval

- Facility
  - On-site

- Electronic Courier / Shipment Organiser

- Facility
  - On-site

- Process
  - Operation

- Staff
  - Theatre
  - Other

- Theatre
  - Other

- Consignment Delivery

- Birth

- Holiday

- Unplanned event

- Time Sensitive Shipments

- Political Affairs

- Natural Disasters

- Competition / Restrictions

- Allele Products
Examples of Root Cause Failures

Physical Conditions
- Vibration
- High Impact (Drop)
- Size
- Contents
- Temperature

Monitoring and Control

Proximity to Product/Sample

Planning and Implementation
- Courier Network
- Single Provider
- Sub-contracted
- Manufacturer
- Courier 3rd Party
- Organiser

GMO Translation (Languages Required)

Locations

Tracking

Chain of Custody Management

By End User

Patient

By Supplier

Therapy Developer

Start

Finish

Route

Time Sensitive Shipments

No. of product or sample units

Vial

T-Flask

Bag

Other

Contents

Data Loggers/ Temp Probes

GMO Standard

Translation (Languages Required)

Documentation

Temperature Monitoring and Control

Temp Control Mechanism

Xeno products

Live Animals

Other Cargo on same Shipment Route

Payload Shock

X-Ray

Tilt

Dedicated

Shared

Scope of Usage

Physic Dimensions

Dewar

Credo Cube

Mini Incubator

Type

Probe Location and Type

Fixed

Free

Moving

Proximity to Product/Sample

Xeno products

Vibration

High Impact (Drop)

Cleaning

Preparation Time

Return to Sender Procedure

Site Management

Package

Product

SHELF LIFE

Manufacturing Release

Clinical Acceptance or Administration Procedures

By End User

By Supplier

Therapy Developer

Locations

Shipping

Temp Control Mechanism
What’s the impact of manufacturing or clinical development teams deciding the product should be cryopreserved?
Case Study B: Mapping Shipping Lanes

What’s the impact on required shipping window / material shelf-life needs as a function of constrained elements within the shipping pathway?

*MC = Manufacturing Centre
## Case Study B: Mapping Shipping Lanes

<table>
<thead>
<tr>
<th>Destination</th>
<th>Original Collection Time (Local)</th>
<th>Original Scheduled Departure Time (Flight or Rail)</th>
<th>First Available &quot;Back-up&quot; Option</th>
<th>New Departure Time</th>
<th>Minimum Additional Shipment Time (h and min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>London</td>
<td>12:00</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Brussels</td>
<td>12:00</td>
<td>14:56</td>
<td>Later Flight - Same Day</td>
<td>16:56</td>
<td>2h 00 min</td>
</tr>
<tr>
<td>Amsterdam</td>
<td>12:00</td>
<td>15:55</td>
<td>Later Flight - Same Day</td>
<td>20:30</td>
<td>4h 35 min</td>
</tr>
<tr>
<td>Paris</td>
<td>12:00</td>
<td>17:13</td>
<td>Later Flight - Same Day</td>
<td>19:13</td>
<td>2h 00 min</td>
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<tr>
<td>Prague</td>
<td>12:00</td>
<td>19:55</td>
<td>Later Flight - Next Day</td>
<td>13:45</td>
<td>17h 50 min</td>
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<td>Warsaw</td>
<td>12:00</td>
<td>15:30</td>
<td>Later Flight - Same Day</td>
<td>20:00</td>
<td>4h 30 min</td>
</tr>
<tr>
<td>Copenhagen</td>
<td>12:00</td>
<td>20:35</td>
<td>Later Flight - Next Day</td>
<td>07:50</td>
<td>11h 15 min</td>
</tr>
<tr>
<td>Houston</td>
<td>12:00</td>
<td>16:25</td>
<td>Later Flight - Same Day</td>
<td>20:20</td>
<td>3h 55 min</td>
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<td>Boston</td>
<td>12:00</td>
<td>19:15</td>
<td>Later Flight - Same Day</td>
<td>22:50</td>
<td>3h 35 min</td>
</tr>
<tr>
<td>Los Angeles</td>
<td>12:00</td>
<td>16:55</td>
<td>Later Flight - Same Day</td>
<td>21:35</td>
<td>4h 40 min</td>
</tr>
<tr>
<td>Tokyo</td>
<td>12:00</td>
<td>01:55</td>
<td>Later Flight - Same Day</td>
<td>11:20</td>
<td>9h 25 min</td>
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<tr>
<td>Tel Aviv</td>
<td>12:00</td>
<td>07:35</td>
<td>Later Flight - Same Day</td>
<td>16:35</td>
<td>9h 00 min</td>
</tr>
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<th>Minimum Additional Shipment Time (h and min)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>13:30</td>
<td>N</td>
<td>1h 30 min</td>
<td>N/A</td>
</tr>
<tr>
<td>Brussels</td>
<td>12:00</td>
<td>19:05</td>
<td>Y</td>
<td>8h 05 min</td>
<td>14h 55 min</td>
</tr>
<tr>
<td>Amsterdam</td>
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<td>21:15</td>
<td>Y</td>
<td>10h 15 min</td>
<td>12h 45 min</td>
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<tr>
<td>Paris</td>
<td>12:00</td>
<td>20:30</td>
<td>Y</td>
<td>9h 30 min</td>
<td>13h 30 min</td>
</tr>
<tr>
<td>Prague</td>
<td>12:00 (+1) 01:25</td>
<td>Y</td>
<td>14h 25 min</td>
<td>8h 35 min</td>
<td>23h 00 min</td>
</tr>
<tr>
<td>Warsaw</td>
<td>12:00</td>
<td>21:50</td>
<td>Y</td>
<td>10h 50 min</td>
<td>12h 10 min</td>
</tr>
<tr>
<td>Copenhagen</td>
<td>12:00 (+1) 02:35</td>
<td>Y</td>
<td>15h 35 min</td>
<td>7h 25 min</td>
<td>23h 00 min</td>
</tr>
<tr>
<td>Houston</td>
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<td>Y</td>
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<td>17h 00 min</td>
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